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BRITISH MEDICAL JOURNAL

LONDON SATURDAY NOVEMBER 12 1955

CAESAREAN SECTION

ITS USE IN DIFFICULT LABOUR IN PRIMIGRAVIDAE*

BY

DUGALD BAIRD, M.D., B.Sc., F.R.C.O.G., D.P.H.

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The discovery of the sulphonamides and the antibiotics has practically removed the risk of fatal peritonitis after caesarean section and has led to the greater use of this operation in obstetrics.

Marshall's (1949) figures showed that even in the years 1943–7 the operation had become comparatively safe. The mortality of the lower segment operation performed at various times after the onset of labour was as follows:

Before or within 6 hours of onset	0.12%
6–24 hours after onset	0.40%
24–48 ,, ,, ,, ...	0.80%
Over 48 hours after onset	2.5%

Clearly, therefore, the risks increase steadily the longer the trial of labour lasts, and are especially high when labour has been in progress for more than 48 hours. In Marshall's series, 66% of all deaths after caesarean section for difficult labour were in primigravidae of 30 years or more, and yet only about 20% of primigravidae are in this age group. In such cases prolongation of labour is usually due to uterine dysfunction or rigidity of the cervix, and the decision to perform caesarean section is postponed in the hope that uterine action will improve. By the time it is clear that caesarean section must be done the labour has lasted so long that the risks of the operation have greatly increased. On the other hand, if less time is given many more caesarean sections will be done and, while the mortality rate will be kept low, just as many women may die because of the great increase in the total number of operations performed. The modern tendency is to avoid difficult vaginal delivery by the greater use of caesarean section in cases of prolonged labour. This is safer for the child and may also be safer for the mother.

Effect of Rise in Incidence

In the City of Aberdeen the incidence of caesarean section rose from 1% in the years 1938–47 to 2.4% in 1948–54. During the first period there were 11 maternal deaths attributable to long or difficult labour out of 29,500 births (3.7 per 10,000 births); five followed caesarean section and six vaginal delivery. In the second period there were four deaths out of 22,000 births (1.8 per 10,000 births); all followed caesarean section. Between 1938 and 1954 the stillbirth rate from birth trauma and anoxia was reduced from 16 to 5 per 1,000 births. Thus, while deaths among babies from these causes have been reduced by two-thirds, maternal death rates have been reduced by a half. Mortality statistics for difficult labour before 1938 cannot be compared with present-day figures, since deaths from shock and haemorrhage could not be distinguished from those due to sepsis, which was a frequent sequel of difficult labour before the advent of the sulphonamides and the antibiotics.

Morbidity is much more difficult to assess, so that we cannot say how far it has been reduced. Fewer difficult forceps operations will decrease the number of cases of laceration of the cervix, vaginal walls, and perineum, and as a result fewer women will have pelvic pain, backache, discharge, incontinence of urine, and prolapse. Late complications of caesarean section, such as incisional hernia, intra-abdominal adhesions, and chronic swelling of the leg from phlebothrombosis, are possibly more common.

It is proposed to discuss this increased use of caesarean section in difficult labour in more detail, using all first births in the City of Aberdeen to avoid the bias which might result from the use of hospital statistics alone.

Fig. 1 shows that in the City of Aberdeen the stillbirth rate fell from 37.6 in 1939–40 to 19.2 in 1953–4. It also shows that the causes† of stillbirth behave differently throughout the period. The death rate from birth trauma and "mature, cause unknown" (unexplained stillbirth of a mature foetus) fell steadily throughout the period, except in 1946–8, while death rates due to "premature, cause unknown" (unexplained prematurity) and ante-partum haemorrhage (this includes placenta praevia and accidental haemorrhage not associated with pre-eclampsia) fell until 1945, but since then there has been a slight tendency for them to rise. We have concluded (Baird, Thomson, and Duncan, 1953) that this fall in the trauma and "mature, cause unknown" death rates is due to increased hospitalization and the increasing use of caesarean section, especially in the case of the elderly primigravida. The temporary rise in the stillbirth rate from these causes in the years 1946–8 was attributed to a great excess of elderly primigravidae immediately after the war and to the fact that because of the high birth rate and the lack of hospital beds many of them were confined at home.

A high standard of technical skill should prevent the more severe forms of birth trauma, especially in the mature foetus, but it is doubtful if the modern obstetrician is any more skilful in the use of the obstetric forceps than his predecessor, so that it seems reasonable to conclude that the great improvement which has occurred is due to the much wider application of this skill and to the avoidance of difficult vaginal delivery by the greater use of caesarean section.

The caesarean section rate in the City of Aberdeen has increased from 0.8% in the years 1938–42 to 2.9% in 1951–4 and in primigravidae from 1.1 to 3.8%. It has been shown by Stewart and Bernard (1954) that the incidence of difficult labour from both mechanical causes and dysfunction rises steadily with the age of the patient, and also that difficult

*Read at the Joint Annual Meeting of the British Medical Association, Canadian Medical Association, and Ontario Medical Association, Toronto, 1955.

†For a definition of the clinical causes of stillbirth used in this paper see Baird, Walker, and Thomson (1954).

labour from both causes increases steadily if pregnancy is prolonged beyond 40 weeks. We have shown (Baird *et al.*, 1954) that, taking the years 1938–52 as a whole, the obstetric death rate (stillbirths + first-week deaths) due to "mature, cause unknown" rose from 2.3 per 1,000 in the 15–19 age group to 19.0 in the 35+ age group, and that "birth trauma" rose from 5.7 in the 15–19 age group to 19 in the 35+ age group. Walker (1954) showed that the obstetric death rate rose quickly after the 41st week and that this was due mostly to an increase in the stillbirth rate, the immediate cause of death being anoxia. The incidence of post-maturity is not influenced by the age of the patient, but the deleterious effect of post-maturity on the baby increases greatly in older women.

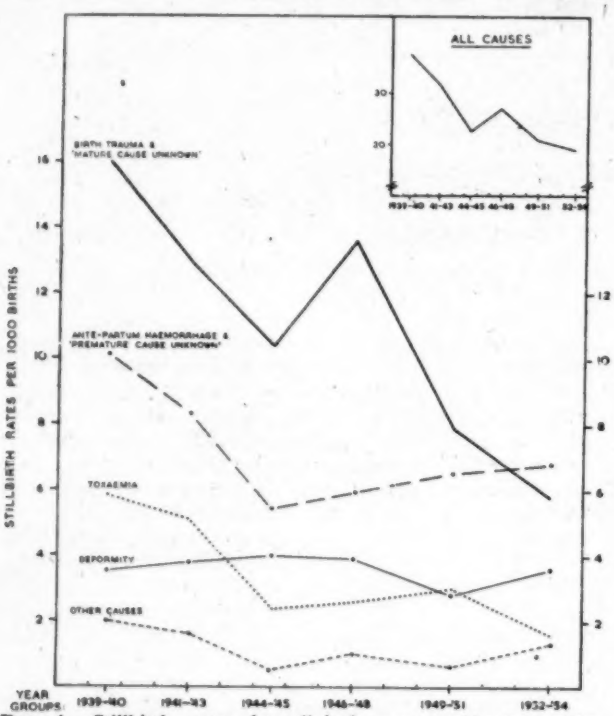

FIG. 1.—Stillbirth rates by clinical cause. Aberdeen City, 1939–54.

A Double Hazard

To sum up, the incidence of difficult labour rises with age, as does the tendency to unexplained intrauterine death of the mature foetus, so that the baby of the elderly primigravida is subjected to a double hazard. In addition, post-maturity increases the chance of a long labour and its dangers. It is not surprising, therefore, that attention was directed to improving results in the older age groups.

Table I shows that a rise in the caesarean section rate in the age group 35+ began in 1943–5, and, as time went on, caesarean section was used more and more in the younger age groups.

TABLE I.—*Caesarean Section Rates*, 1938–54. *Aberdeen First Maternities*

	Age at Delivery				
	16–19	20–24	25–29	30–34	35+
	%	%	%	%	%
1938–42	—	0·6	1·2	1·6	4·0
1943–45	0·5	0·3	1·6	1·7	6·0
1946–47	—	0·6	1·5	2·6	8·3
1948–50	0·3	1·0	3·0	5·3	20·9
1951–54	0·8	1·3	3·7	9·1	27·3

Fig. 2 shows graphically the caesarean section rate by age in primigravidae and the combined stillbirth rate from "birth trauma" (Tr.) and "mature, cause unknown" (M.U.) in three periods of time—1938–47, 1948–50, and 1951–4.

During the years 1938–47 the combined Tr. and M.U. rate in primiparae rose very quickly with age, from 7.5 in the age group 15–19 to 40 in the age group 35+. By the years 1948–50 the rate at all ages from these causes had fallen from 17.2 to 12.3 per 1,000, and the improvement was most marked in the age group 35+. During this time the caesarean section rate in this age group had increased from an average of about 6% to 20.9%. In primigravidae, aged 35 and over, for each 100 births 1.5 stillbirths due to M.U. and Tr. had been prevented at a cost of 16 additional caesarean sections. If no other factors enter into the picture, it appears as if ten additional caesarean sections had saved only one baby from being stillborn because of "trauma" or "mature, cause unknown." In the age group 30–34, the stillbirth rate from these causes did not fall although the caesarean section rate rose from 1.8 to 5.1%. This suggests that up to 1950 the methods of selection of cases requiring caesarean section were not very precise, and that from the point of view of preventing death of the baby many caesarean sections had been done unnecessarily.

Between 1948–50 and 1951–4 the stillbirth rate from Tr. and M.U. fell from 12.3 to 6.3 per 1,000, and the caesarean section rate rose from 2.7 to 3.7%. Fig. 2 shows that there was a fall in stillbirths at all age groups except 15–19, and that it was most striking in the age groups 30–34 and 35+. In the case of the age group 35+ the stillbirth rate fell from 25 to 0, and during this period the caesarean section rate rose from 20.9 to 27.3%, a much smaller increase than in the previous period. In the age group 30–34 the stillbirth

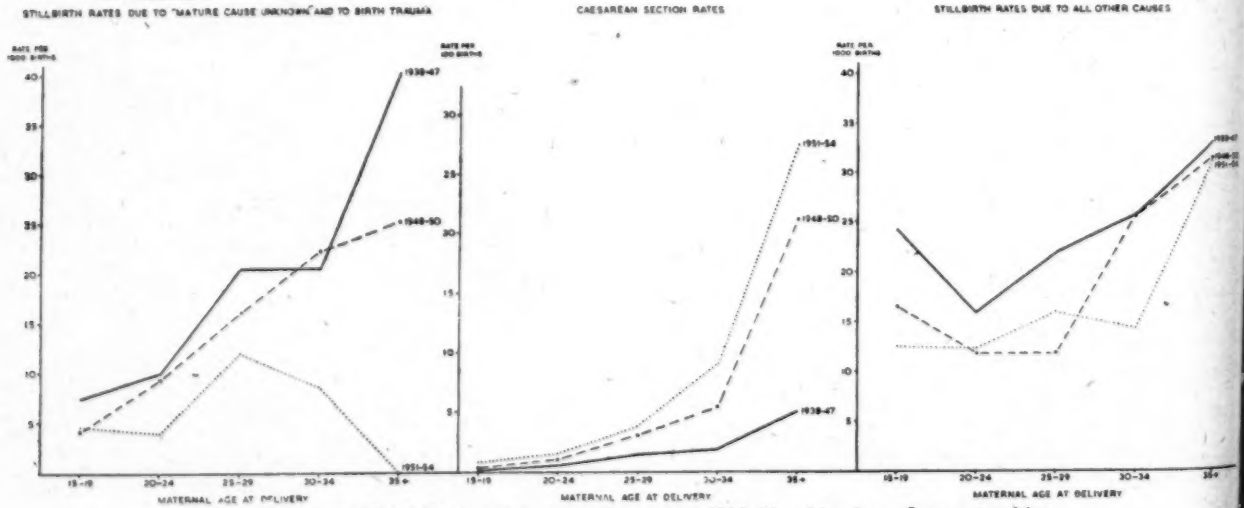
STILLBIRTH RATES DUE TO "MATURE CAUSE UNKNOWN" AND TO BIRTH TRAUMA
CAESAREAN SECTION RATES
STILLBIRTH RATES DUE TO ALL OTHER CAUSES
1938–47
1948–50
1951–54
MATERNAL AGE AT DELIVERY

FIG. 2.—Stillbirth and caesarean section rates, 1938–54. Aberdeen, first maternities.

rate fell from 22 to 8, and the caesarean section rate increased from 5 to 9%. In both of these age groups it appears that only two or three additional caesarean sections were necessary to prevent one stillbirth. This suggests that the method of selection of cases for caesarean section improved considerably after 1950.

Fig. 2 shows that the increased use of caesarean section in the older age groups has not affected the stillbirth rate from other causes. Nevertheless the "trauma" and "mature, cause unknown" deaths form such a large proportion of the total stillbirths in these older age groups that their virtual elimination has completely altered the graph of stillbirth rates by maternal age, which no longer rises steeply.

The stillbirth rates in each five-year age group, starting with the youngest, are 17, 16, 28, 23, and 31.

Reason for Improved Stillbirth Rates

The reason for the striking improvement in the stillbirth rates in the period 1951–4, especially in primigravidae over 30 years of age, will now be examined in more detail.

Because of the increasing awareness of the dangers of post-maturity, especially in the elderly primigravidae, a policy of induction of labour at the end of the 41st week of pregnancy has gradually developed. In the years 1951–2 artificial rupture of the membranes, as a method of inducing labour, was used in those cases in which it was thought that clinical signs of "post-maturity" existed, such as loss of weight or decrease in the amount of liquor amnii, and was not usually performed before the end of the 42nd week. In the years 1953–4 it became a routine procedure in all primigravidae of 25 years or more when pregnancy had reached the end of the 41st week.

One advantage of puncturing the membranes was that it allowed meconium staining of the liquor to be detected, thus giving warning that a certain degree of anoxia already existed in the foetus (Walker, 1954).

Caesarean section was performed no more frequently for difficult labour in 1951–4 than in 1948–50, but on the whole the length of the trial of labour was reduced. For example, the percentage of caesarean sections for difficult labour performed after more than 48 hours of labour was reduced from 40 to 25. The shortening of the length of the trial of labour was most marked in primigravidae of 30 years or more.

Table II shows that a trial of labour lasting 48 hours or more is most frequently allowed in the age group 25–29. In those under 25 years of age uterine dysfunction is less common and disproportion is most often the cause of the difficulty. For this reason a decision for or against caesarean section is made sooner than in the 25–29 age group, where the difficulty is more often due to disordered

TABLE II.—*Length of Labour Before Caesarean Section*, 1951–4. *Aberdeen Married Primigravidae*

Age at Delivery	Length of Labour before Caesarean Section				Total No. of Cases
	Elective −6 Hrs.	−24 Hrs.	−48 Hrs.	48 Hrs.+	
	%	%	%	%	
−25	10·0	30·0	45·0	15·0	40
25–29	32·5	12·5	27·5	27·5	40
30–34	50·0	25·0	18·8	6·2	32
35+	62·9	14·3	20·0	2·8	35

uterine action or rigidity of the cervix. Disproportion is less common in the 25–29 age group, since primigravidae in this age group come much more frequently, in Britain at least, from the upper social classes and are tall, well-grown, and have a roomy pelvis. The patient is still young enough to make one hesitate to perform a caesarean section in the first labour, since it may deter her from having another child and may complicate a second labour. Nevertheless the deleterious effect of age on intrauterine physiology has begun to operate in this age group, as shown by the fact that the stillbirth rate in the "mature, cause unknown," group is rising. Even in the 1951–4 period the M.U. stillbirth rate is three times as high in the 25–29 as in the 20–24 age group. These facts may explain why the combined trauma and "mature, cause unknown" stillbirth rate in the years 1951–4 is highest in the age group 25–29 (Fig. 2).

In the age group 30–34, 50% of the caesarean sections are performed before the onset of labour and only 6% after a labour of 48 hours.

It was thought that routine induction of labour at the end of the 41st week in all primigravidae over the age of 25 might prevent some cases of long labour on the basis that the uterine action might be better at 41 weeks than a week or so later, and the baby, being less anoxic at the onset of labour, would be less likely to show signs of distress during labour. In actual fact the policy has had the opposite effect—namely, an increase in the caesarean section rate. This is probably due to the fact that when puncture of the membranes is performed the liquor is already sometimes stained with meconium or becomes stained. The passage of meconium when the vertex presents has been shown by Walker to be associated with a falling oxygen supply to the foetus, and should the onset of labour be unduly delayed after the puncture of the membranes or labour be rather prolonged, caesarean section has been performed sometimes "to be on the safe side." Although the overall caesarean section rate increased from 2.8% in 1951–2 to 4.7% in 1953–4 there was no corresponding fall in the stillbirth rate from trauma and "mature, cause unknown." Judged by stillbirths the increased caesarean section rate in the last two years may not have been justified, but the possibility of non-lethal effects of anoxia have to be considered.

The number of cases studied so far is too small for firm conclusions to be arrived at as to the value of induction of labour in post-maturity and the optimum caesarean section rate in primigravidae. Probably the figure should be somewhere between 3 and 5%, but it must be emphasized again that the rate depends on the age composition of the group under consideration.

Table III shows that in the period 1938–47, 113 out of 145 (78%) of caesarean sections in primigravidae were performed for difficult labour and abnormal presentation, and

TABLE III.—*Obstetric Deaths in Caesarean Section Cases by Cause. Aberdeen First Maternities (Single Births)*

Reason for C.S.	1938–47		1948–54		Total	
	Obstetric Deaths	No. of C.S.	Obstetric Deaths	No. of C.S.	Obstetric Deaths	No. of C.S.
Difficult labour ..	2	87	5	133	7 (3·2%)	220
Abnormal presentation	2	26	2	20	4 (8·7%)	46
Foetal distress ..	0	3	2	27	2 (6·7%)	30
Age and infertility	0	4	2	17	2 (9·5%)	21
Placenta praevia and accidental haemorrhage ..	3	10	2	13	5 (21·7%)	23
Toxaemia	0	5	1	14	1 (5·3%)	19
Gynaecological condition ..	0	5	0	4	0 —	9
Maternal disease ..	0	5	3	10	3 (20·0%)	15
All reasons ..	7 (4·8%)	145	17 (7·1%)	238	24 (6·3%)	383

few for other causes, but since then more have been done for age and infertility and foetal distress. It will be seen also that in the latter period the obstetric death rate (stillbirth + first-week death rates) in caesarean section cases has risen. This is due to the fact that in the earlier period caesarean section was seldom performed, except in cases of placenta praevia, unless the baby seemed healthy, but now it is performed in the hope of saving the baby, sometimes even when the signs point to the fact that foetal distress is already present. It is not surprising that in a few cases anoxia has been too severe or too prolonged and the baby has died despite caesarean section.

Analysis of the deaths (stillbirths and first-week deaths) in the years 1951–4 shows that with regard to the group

"mature, cause unknown," 5 out of 26 occurred after the completion of the 42nd week of pregnancy—3 out of 1,063 primigravidae in the 25–29 age group, and 2 out of 2,272 in the 20–24 age group. There is therefore still, theoretically at least, a little scope for a reduction in the number of deaths from post-maturity in the 25–29 age group. The majority of unexplained deaths now occur at or about term and cannot be avoided in the present state of knowledge. Out of 22 deaths from birth trauma only one occurred after the end of the 42nd week. Labour lasted less than 24 hours in 15 cases and more than 48 hours in only 4. Eight of the 22 deaths were attributed to the cord being prolapsed or twisted tightly round the baby's neck; 6 occurred with breech delivery (complicated by prematurity in 3 cases). Nine of the women were under 5 ft. 1 in. (155 cm.) in height, and 13 between 5 ft. 1 in. and 5 ft. 3 in. (155 and 160 cm.). There were none over 5 ft. 4 in. (163 cm.). The danger of labour in small women is thus emphasized, especially when the age factor has begun to operate to produce rigidity of the pelvic bones, rigidity of the cervix, and the predisposition to intrauterine death.

Table I shows that between 1948–52 and 1951–4 the caesarean section rate in the age group 25–29 rose only slightly, from 3.0 to 3.7%. Possibly more caesarean sections should be done in this age group to bring the foetal death rate into line with that of the age group 30–34.

It has been stated (McKeown, 1954) that probably the optimum time to have a first baby is between the ages of

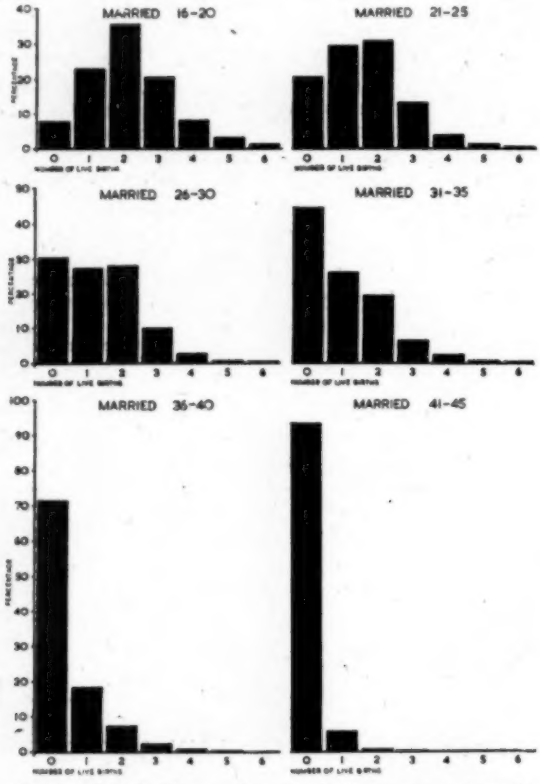

FIG. 3.—Family size at the end of 10 years' marriage, by age at marriage, for 1939 cohorts (Taylor, 1952. Reproduced by permission of the author and of the publishers).

25 and 30, because, while labour may be more difficult, the infant mortality is low, indicating that the children of such mothers are well cared for. The risks of postponing child-bearing even to this age are shown in Fig. 3, which illustrates that maximum fertility is retained for a relatively short time. After ten years of marriage the percentage of women still childless is least in those who married before the age of 20 and increases very quickly thereafter. Of those who married between the ages of 25 and 30, 30% have not had a child in ten years of marriage, 28% have had only one child, and only 15% have had more than two. A stillbirth may therefore increase greatly the risk of childlessness. It may, of course, stimulate the couple to replace the lost baby by another more quickly than they would have had a second child, if the first had survived. There is some evidence that this does in fact occur. For example, in a series of private patients, it was found that 67% of second births took place within two years of a first birth which resulted in a stillbirth, whereas when the first baby survived, the second birth occurred within two years in only 38% of cases. Conversely, the second birth was delayed for more than four years in only 10% of cases where the first baby was stillborn, and 28% of cases where it was born alive.

I do not know how many women whose first child was stillborn did not have a second pregnancy at all. In young women the loss of a first child is less likely to limit the size of the completed family, and if the first child is born by the vagina, even after a long and difficult labour, subsequent labours are usually easy. On the other hand, caesarean section performed in the first labour, even in a young woman, might necessitate caesarean section next time, and this might limit the family size, since most women who have undergone two caesarean sections prefer not to have more children and often ask to be sterilized after the second. In the age group 30+ this policy would not limit the family size, since few women who have a first child at 30 years or more have more than two children under any circumstances.

An Important Point

It is important to determine, particularly in young women, whether a caesarean section in the first labour will decrease the likelihood that the mother will have a second baby. To test this, all hospital-booked primigravidae who were delivered by caesarean section in 1948–50 have been followed up for four years, along with two control groups consisting of an equal number of women, (1) who had a forceps delivery, and (2) who had a spontaneous delivery in 12 hours or less. Cases in each group were matched in pairs, for age, height, social class, and length of marriage before the first birth.

Table IV gives the results of an analysis of 48 women who had a first child by caesarean section and 48 individually matched cases in which there was a spontaneous

TABLE IV.—*Child-bearing After Caesarean Section**

Spontaneous Delivery Cases: Subsequent Children	Caesarean Section Cases: Subsequent Children		Total
	At Least One	None	
At least one ..	9	14	23
None	4	21	25
Total	13	35	48

* This Table summarizes the results of a four-year follow-up of a matched series of caesarean section and spontaneous delivery cases (48 in each group). The numbers summarize information provided by each pair of cases. Thus, for example, 14 in the top right-hand corner signifies that, in 14 pairs, women after caesarean section had no subsequent children within the four years, while their spontaneous delivery controls had at least one child in this period.

delivery in under 12 hours. It is seen that 14 of the caesarean section cases had not had another baby, while each of their matched spontaneous delivery controls had at least one. Only four who had spontaneous deliveries had not had another child, while their matched caesarean section cases had had at least one. Numbers are too small to permit a conclusive analysis of subgroups, but it seems that a similar disparity occurred in each age group and in each social class. It also held both when the caesarean section was elective and when it was done after a trial of labour. Caesarean section seemed to have its deterrent effect even in cases of pre-nuptial conception where little conscious planning of the first pregnancy had been shown. This might mean that the relative infertility after caesarean section was involuntary and acted through a physical mechanism in the pelvis unconnected with the patient's emotional reaction to the

caesarean section, or it might be that young women, usually in the lowest-income group, many of whom make no effort to plan their marriage and first pregnancy, were just as deterred by a previous caesarean section as those, usually in the upper-income group, who had given the matter a great deal of thought. Indeed, young badly educated women might be more easily frightened by an abdominal "operation" performed unexpectedly in labour than the better-educated elderly primigravida who knows that, because of her age, caesarean section is a likely occurrence which may be the only means of saving her baby.

When the effect of forceps delivery was tested against spontaneous delivery by the matching technique mentioned above, no deterrent effect of the forceps delivery similar to that of caesarean section could be detected. It seemed that the length of the labour before the forceps delivery also had no demonstrable effect in deterring the women from having another child. Caesarean section appears, therefore, in Aberdeen at least, to have a deterrent effect which is not found after any form of vaginal delivery.

Conclusions

A healthy well-oxygenated baby is very little affected even by a prolonged and difficult labour unless undue force is applied to the head in the course of an instrumental vaginal delivery. In healthy well-grown young women the pelvis is normal, uterine function is usually very good, and labour is therefore easy as a rule, and, in addition, placental function is so good that only the most extreme forms of post-maturity will cause dangerous anoxia.

From the age of 25 placental function becomes steadily less efficient, especially if pregnancy goes beyond 40 weeks. In addition, disordered uterine action and rigidity of the cervix also become more common, so that the risk of fatal anoxia is much increased. The avoidance of post-maturity by induction of labour will lessen the risk of anoxia but will not remove it. In our experience it has not led to a reduction in the use of caesarean section, but it has led to a reduction in the stillbirth rate. Unfortunately no specific test can be used to measure the risks of stillbirth in any particular case, so that one must decide the line of treatment on probabilities. In some cases there is a heaping up of unfavourable factors. For example, the outlook is very unfavourable in the primigravida over the age of 30 who is under 5 ft. (152 cm.) in height, especially if the pregnancy goes beyond 41 weeks and if the head is lying in the occipito-posterior position. If, in addition, there is pre-eclampsia or hypertension, or other serious maternal disease, the risks of a stillbirth are great and a caesarean section is justifiable. We do not believe that rupture of the membranes is harmful in most of such cases, since labour will often come on soon and progress favourably and will thus greatly diminish the need for caesarean section, which could, however, still be done with safety if required.

What is wanted is the lowest stillbirth rate and the lowest caesarean section rate. In our experience the optimum caesarean section rate is between 3 and 5% in primigravidae. This will depend on the age composition of the women being treated and the standard of health and nutrition in the community. It is important to study a "total" population to eliminate bias, otherwise percentages may be most misleading—for example, if they are derived from a hospital series only.

Summary

The methods of assessing the condition of a foetus *in utero* are at present very imprecise, and therefore the decision to deliver by caesarean section in the interests of the child's life is far from easy. If the operation is delayed until labour is well advanced, the risk for both mother and child is increased: on the other hand, early caesarean section in anticipation of danger means that the operation may have been unnecessary. Although the operative risks are small, the total maternal deaths may be just as great with many operations carrying a low mortality as with few operations carrying a high mortality risk.

These problems have been examined by comparing the trends in caesarean section rates and in stillbirth and maternal mortality rates in Aberdeen primiparae. The stillbirth rates from birth trauma and unexplained intrauterine death fell by two-thirds and the maternal mortality from difficult labour by half between the years 1938 and 1954. These reductions are attributed to (*a*) increased hospital confinement, (*b*) more extensive use of caesarean section, especially in primiparae over the age of 25, and (*c*) the avoidance of the effects of postmaturity by induction of labour shortly after term.

There is no doubt that recognition of the hazards of postmaturity has contributed substantially to the fall in the stillbirth rate, but the ideal practice is not easy to determine. Routine surgical induction of labour in primiparae aged 25 or over not delivered by the end of the 41st week has not had a demonstrably better effect on the stillbirth rate than a policy of induction only in cases with "clinical" evidence of postmaturity. Again, undue anxiety about the signs of foetal distress may lead to unnecessary caesarean sections. In terms of total family size the long-term deterrent effect of caesarean section on future births has to be sent against the immediate saving of infant lives.

A follow-up study has shown that a first pregnancy ending in caesarean section has a deterrent or delaying effect on further pregnancies, compared with first pregnancies ending in spontaneous or forceps delivery. In the young primipara, the acceptance of some slight risk at the first delivery may be justified in the interests of future fertility, whereas in the "elderly" primipara it may be of primary importance to secure a live first birth at all costs.

References

Baird, D., Walker, J., and Thomson, A. M. (1954). *J. Obstet. Gynaec. Brit. Emp.*, **61**, 433.
—— Thomson, A. M., and Duncan, E. H. L. (1953). Ibid., **60**, 17.
McKeown, T (1954). *Med. Pr.*, **232**, 310.
Marshall, C. M. M. (1949). *Trans. 12th Brit. Congr. Obstet. Gynaec.* Austral Press, London.
Stewart, D. B., and Bernard, R. M. (1954). *J. Obstet. Gynaec. Brit. Emp.*, **61**, 318.
Taylor, Wallis (1952). *Brit. J. soc. Med.*, **6**, 226.
Walker, J. (1954). *J. Obstet. Gynaec. Brit. Emp.*, **61**, 162.

At a meeting of the Harveian Society of London on October 12, Dr. DESMOND CURRAN, senior psychiatrist at St. George's Hospital, talked on murder. His discourse was based on a large series of patients, found guilty of the crime, in whom varying degrees of insanity had been responsible for their actions. As a more satisfactory alternative to the death penalty, he suggested detention in a mental institution or prison where the murderer's mental health could be reviewed periodically. If necessary confinement would be permanent; such a sentence was not remarkable to a psychiatrist, he said, who was accustomed to permanently institutionalized patients. If, on the other hand, the murderer regained his mental health, he could be granted supervised parole. The argument that such a paroled murderer is apt to revert to further homicide was not supported by facts. Only one Broadmoor patient had ever relapsed in this way. This was in noteworthy distinction from other types of criminals, and might be due to the well-defined motivation of the murderer, who displayed no remorse for his particular victim. If the death penalty were abolished, said Dr. Curran in conclusion, the present somewhat metaphysical questions of the M'Naghten Rules should be superseded by the more practically important ones: Would the murderer get better, and what would be his response to treatment?

THE PROTECTION OF INFANTS AGAINST TUBERCULOSIS*

BY

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During the past five years we have vaccinated 7,115 people. This may seem a very inadequate number on which to base any firm conclusions, but all the newborn infants (5,215) have been seen personally by Dr. Margaret Griffiths or myself and, so far as is possible with a changing population, followed up yearly, so that many infants have already had their fourth annual check-up and tuberculin test as well as repeated chest *x*-ray examinations. What we primarily tried to achieve was the eradication of progressive (and fatal) disease in the first few years of life.

Between 1949 and 1954 there were 50 deaths from tuberculosis in Manchester in children under the age

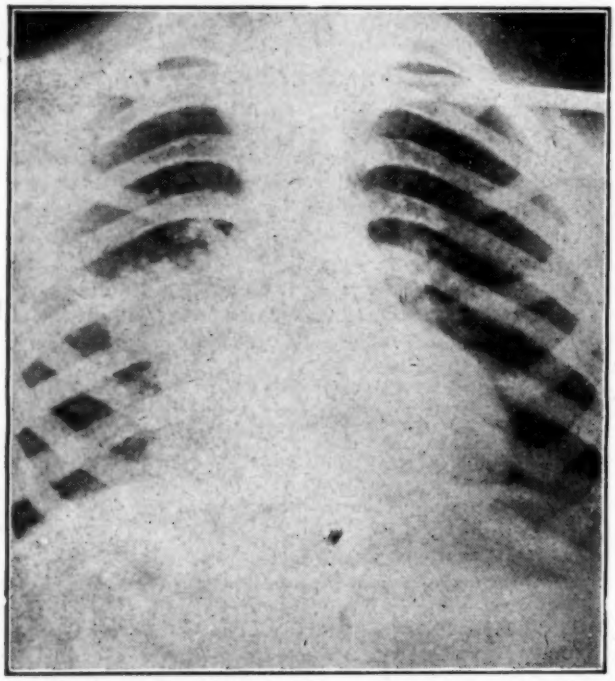

FIG. 1.—*X*-ray film of chest of child with primary tuberculosis.

of 5 years, of whom 12 were under 1 year old. There may well have been others, not certified as due to tuberculosis. No deaths from tuberculosis have occurred in our 5,215 vaccinated newborn babies—and 537 (just over 10%) of them were known contact cases: in addition, there were another 250 known contacts between the ages of 1 month and 2½ years and more than 100 over that age—nearly 1,000 in all. There were also 28 mothers who developed tuberculosis (or it became clinically evident) after their infants had been vaccinated, yet, despite their not having been segregated, none of these infants developed tuberculosis. Furthermore, no radiological lesions of tuberculosis have been seen in any vaccinated children from tuberculous homes during the four-year follow-up, whereas there have been

*The second of the 1954–5 Leonard Parsons Memorial Lectures, delivered to the Faculty of Medicine, Birmingham University, on May 12. The first lecture was printed in last week's issue.

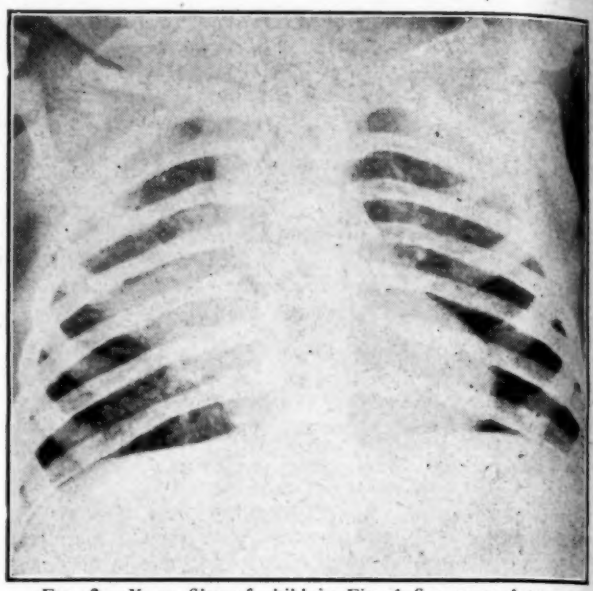

FIG. 2.—*X*-ray film of child in Fig. 1 five years later.

13 infants born at St. Mary's Hospital or on the district during the same time who developed primary tuberculosis; none of these had been vaccinated. In our contact families almost exactly half of the patients were suffering from active tuberculosis and in half the disease was quiescent. The percentage of parents accepting vaccination for their newborn infants has been approximately 40%; the remainder serve as unwitting controls, and it was from among these that the 13 tuberculous cases came.

Even in older children primary infection cannot always be regarded lightly, for the lesion may be long-lasting, as shown by the two *x*-ray films (Figs. 1 and 2), taken five years apart (with intervening ones unchanged), and such children are at risk all this time, particularly from such infections as measles and whooping-cough and also from any debilitating condition. In addition, this type of case provides a large proportion of the cases of bronchiectasis seen in later childhood. It is problems such as these that make a consideration of the advisability of using isoniazid germane.

Contacts

Fig. 3 brings to light another problem. Although we had nearly a thousand known contact cases it is impossible

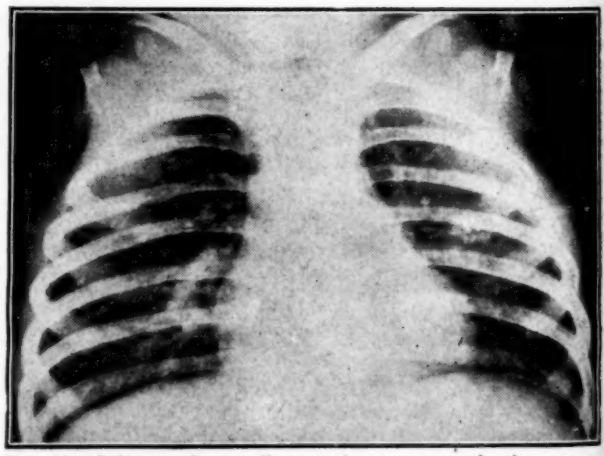

FIG. 3.—Primary focus discovered at pre-vaccination *x*-ray examination.

to estimate the number of unknown contacts. This is the picture found in a child aged 17 months, who was the sister of one of our vaccinated infants. She attended with her sister, who was due for a follow-up tuberculin test, and was tested at the same time because the mother wished her to be vaccinated also; but she was found to be Mantoux positive. An *x*-ray film was then taken (Fig. 3). The mother gave us no history of contact, but in the light of this film the tuberculosis authorities were informed and replied promptly that the father was known to them as a phthisical patient who had taken his discharge from a sanatorium against advice. The vaccinated infant, happily, remained well.

Children with home contacts are undoubtedly at greater risk. Bentley *et al.* (1954) estimated that 5.3% of all children in London lived in tuberculous households. Dr. M. J. Greenberg kindly gave me the comparable figure for Manchester—it was 5.6%. In Birmingham conditions would appear to be a little better. Dr. V. H. Springett estimates the figure at 4%, and I am indebted to him for his assessment, and also for pointing out that this type of calculation can clearly provide only a very rough estimate, because of the difference between the age–sex distribution of the family contacts and that of the population in general, and because it applies to all children under the age of 16 years and not to the restricted period of infancy which I am discussing. With regard to Birmingham, Dr. Springett further pointed out that there may well be differences in the distribution of family sizes between the city and the region as a whole.

Nevertheless it is interesting how closely the figures agree; they at least give some indication of the extent of the risk of the child population in general in England's three most important cities.

Jachnis (1947) recorded a mortality of 9.5% from tuberculosis among 378 infants and children under the age of 4 years who came from tuberculous households. It is fair, therefore, to assume that there should certainly have been *some* deaths from tuberculosis by now among our vaccinated contact infants if the vaccination had not been effective.

It is an accepted fact that the younger the child the greater the mortality; the zenith is reached in congenital tuberculosis, and more than one-fifth of all deaths from non-respiratory tuberculosis occur in the pre-school years. Mitchell and Willis (1944) reported in a series of 243 children under their care in a Detroit sanatorium that there were 29% of deaths in the infants under 19 months of age as compared with 10.5% between that age and 3 years. Jorup (1946), in Sweden, recorded a 60% mortality in those infected in the first three months of life, and this is not an exaggerated figure, taking the literature throughout, although to-day's mortality is undoubtedly lower, following the introduction of isoniazid.

What is even more serious is that in Stockholm, which is renowned for its tuberculosis services, Söderling (1939) found that the infants under 2 years of age who were infected owed this to previously undiscovered tuberculous adults. This is the risk which is ever present—one simply *cannot* exclude the casual contact with an unsuspected adult with open tuberculosis.

"It is paradoxical that where the tuberculosis services are best the risk to infants is greatest because it almost certainly comes from an unexpected, and unsuspected, source—whereas appropriate arrangements for segregation and a high standard of hygiene are likely in most of the families known to the tuberculosis authorities" (Hewell and McClellan, 1954).

Development of Immunity

In the newborn period—with which, as I said, we have been particularly concerned in our studies in Manchester—the development of immunity and the placentally transmitted immunity and the possibility of the absorption and utilization of antibodies by the ingestion of colostrum have been extensively studied. It is generally agreed that there can be some degree of immunity placentally transmitted against certain infections, such as poliomyelitis and measles. It is also the consensus of opinion that colostrum is practically valueless as a source of immune bodies in infancy. The great protective value of breast-feeding is in eliminating the risk of bovine infection from unclean or infected cows' milk, and this, of course, applies to tuberculous as well as other milk-borne infections.

The powers of independent immunity development in the newborn are generally thought to be very poor. For this reason diphtheria prophylaxis and other like measures are usually postponed till the age of 4 to 6 months. In the case of diphtheria it is well known that if the mother is Schick-negative the development of immunity in the infant following toxoid is inhibited for some weeks by the passively transmitted antitoxin.

Rollof and his associates (1954) have suggested that a similar mechanism exists in tuberculosis, for they found that newborn infants of tuberculous mothers were slow to respond to B.C.G. vaccination and that they reverted more readily. By serological studies, using the Middlebrook-Dubos haemagglutination titres, they showed that the antibody did not pass across the placenta, but thought the delayed response was due to passively transferred immunity in some other way. It is interesting to note that Ström, in his studies on radioactive B.C.G., showed that newborn infants vaccinated with B.C.G. possessed the ability to localize the organisms at the site of vaccination to some extent even before Mantoux conversion, and this supports the opinion that there may be some passively transferred immunity already existing at birth. Antibodies are certainly present in the liquor, and the foetus drinks this in abundance from about the fourth month onwards; he therefore has ample opportunity to acquire some immunity before birth. Hagberg (1954), in investigating contact newborn infants, reported, like Rollof, that their conversion rate was much slower than in non-contact infants. Our figures have been quite contrary, for 97% of our contact infants had converted by four weeks compared with 81% in the non-contact cases.

In considering the suggestion of delayed conversion in general in the newborn, Hewell and McClellan (1954) reported findings identical with ours—that their highest conversion rate occurred in this age group, and, furthermore, that the least change in sensitivity with the passage of time was in this group; with this we also agree.

Duration of Tuberculin Sensitivity

The actual duration of sensitivity we do not yet know. After four years our number of reversions is still extremely small. The latest report from Sweden, a careful seven-year study by Enell (1955), showed that, of infants vaccinated at birth with the attenuated Swedish vaccine, 85% were still positive after seven years. For schoolchildren whose average age at vaccination was 7½ years the figure was 91% at the end of the ninth school year, but for schoolchildren the chances of exogenous superinfection and consequent allergy boost are of course greater than in infants.

We have used in general 100 T.U.—that is, 1/100 O.T.—in our Mantoux tests to reach our conversion figures of 100%, and this draws attention to the work of Palmer

et al. (1954) on non-specific tuberculin sensitivity. They maintain that only reactions to 5 T.U. can be regarded as specific. However, in our series, although more of the initial post-vaccination Mantoux tests have been with 100 T.U., we have repeatedly found positives with 10 T.U., and those reacting to 100 T.U. very strongly, as many have, rapidly show an equally good response to 10 T.U. These non-specific reactions are much less likely to be significant in newborn infants than in adults or even older children.

In this country 100 T.U. is the generally accepted strength for pre-vaccination testing, and if greater dilutions are used and a negative reaction is accepted as indicating freedom from past infection, a number of Koch phenomena may occur after vaccination, suggesting that the individuals so reacting had, in fact, already been infected.

Heaf (1955) drew attention to the high reversion figures he obtained, and suggested that this might be explained on the basis of local desensitization of the skin to tuberculoprotein following a previous Mantoux test; but we have not experienced this phenomenon, having seen only 14 reversions (and 6 of these were with freeze-dried vaccine, which is notable for its varying antigenicity) among all our newborns. Reversion is commoner after scarification and multiple puncture techniques, and the fewer complications after such vaccinations are undoubtedly due to the smaller quantity of vaccine absorbed, with diminished multiplication of the bacilli *in vivo*, lower allergy, and lower immunity. One must always pay more for the best—and the price of intradermal vaccination, at least in the newborn with a potent vaccine, is an increase in scars, though this is now reduced to a reasonable proportion and depends almost entirely on the individual susceptibility of the infant concerned. Biering-Sorensen (1953) reported an excessive number of abscesses following vaccination in the newborn in a maternity hospital in Copenhagen, and questioned whether this incidence of complications was sufficient to discountenance vaccination at this age or whether scarification should replace the intradermal route.

The number of complications reported to the Ministry of Health, showing this marked preponderance of these complications in the newborn, may be explained, at least in part, by the fact that these reports, which are from many thousands of vaccinations, nearly all occurred in the early days of B.C.G. in this country, and the thigh was used regularly initially until it was realized to be unwise, and the dose used at that time was much more than that which we now know to be necessary to ensure conversion.

Vaccine Dosage in the Newborn

We have stressed before (Gaisford and Griffiths, 1954) that newborn infants do not require twice as much as older children or adults, and that this is a dangerous recommendation when a potent vaccine is used. It is based on Wallgren's work, which referred directly to the Swedish vaccine —a much more attenuated one than the Danish. Half the adult dose is all that is required in the ordinary newborn infant, so that almost all these cases reported to the Ministry were likely to have received four times the optimal dose, and this with a highly antigenic vaccine—the Danish B.C.G. The only occasions when we vary our dose are when known contact infants are to be vaccinated, and even then only half the Ministry-recommended dose is given; we are now inclined to believe that this is not really necessary, for the immunity may well depend on the active multiplication of the organisms rather than on their initial numbers. With a really potent live vaccine a very few organisms may rapidly multiply *in vivo* and produce a better and longer-lasting effect than two hundred or more times the initial number of more attenuated bacilli.

Although scarification produces fewer complications it is completely inaccurate regarding the dose absorbed, and does not compare with the intradermal route for controlled trials. The same applies to vaccination by aerosol, which has been used in France by Maclouf and Fichez (1952), who found that five minutes' inhalation of B.C.G. produced conversion regularly, and to oral vaccination, which, despite the "hit and miss" effect of this method, is followed routinely, and compulsorily, in Russia, where every newborn infant is so treated, and in Brazil, where Rosemberg (1954) reported that there had been no cases of tuberculosis among 401 newborn infants given six doses of B.C.G. by mouth at monthly intervals. These infants all lived in a tuberculous environment in Rio de Janeiro and São Paulo (cities with very heavy tuberculosis morbidity rates). It may be recalled that, when first used for the vaccination of infants by Weill-Hallé as long ago as 1921, the B.C.G. was given by mouth.

Complications

With regard to complications, I have nothing much to add to our previous publications on this aspect except to say that they are now rare (0.3%) and that we have seen no other untoward effect than local or nodal sinus formation.

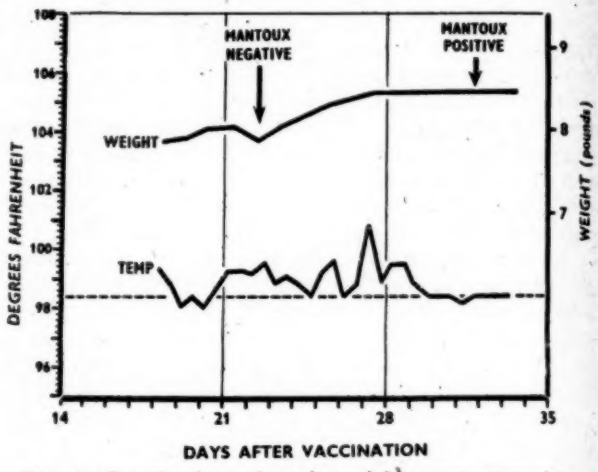

FIG. 4.—Pyrexia observed at time of Mantoux conversion.

Included in our series were 40 pairs of twins. It was interesting that in "like" twins the size of the local reaction and the area of induration of the post-vaccination Mantoux test were identical and that when one twin developed a regional adenitis the other one showed corresponding enlargement of similar nodes.

While it cannot be regarded as a complication, or even untoward, an interesting occurrence was observed occasionally. During their in-patient stay for segregation, contact-vaccinated newborn infants were subject to the same routine as other infants, and this included temperature recording. It was noted that for no apparent reason some of them became mildly

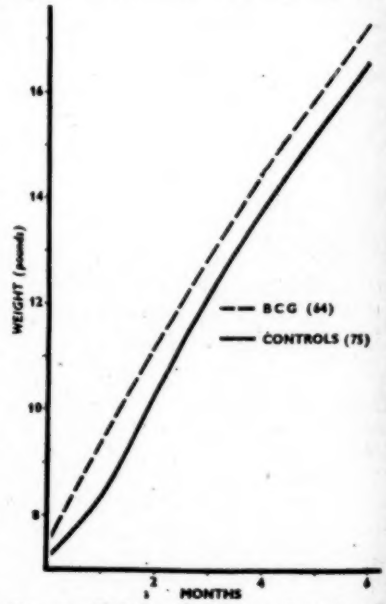

FIG. 5.—Weight gain in vaccinated and control infants.

pyrexial for a few days—without signs of any sort—and this may well have been due to the mild febricula of initial B.C.G. infection, which passes unnoticed in the home. The fever coincided with the change-over to a positive tuberculin reaction (Fig. 4).

It has been stated that a slowing of weight gain occurs in vaccinated infants. In a series in which we investigated this we found no such effect (Fig. 5).

In view of the experimental suppression of vaccination in animals by the concurrent administration of isoniazid it has been interesting to observe those infants who, at or about the time of vaccination, were given streptomycin because of some neonatal infection. No suppressive effect was evident, which might be considered as evidence in favour of the superiority of isoniazid over streptomycin, but most likely it was that the streptomycin, being given for a relatively short time, could hardly have been expected to affect the action of the B.C.G.

After a well-marked adenitis, calcification in the axillary region is commonplace, but in our serial follow-ups we have seen no intrathoracic calcification, although when we used the thigh for the injections originally, and inguinal calcification was frequent, we occasionally saw calcification extending to the deep iliac glands.

Calcification lasts for a long time, though there is a tendency to gradual diminution in size. Where the glands are much enlarged calcification later is the rule. Where the glands break down and discharge calcification is subsequently much less evident. Calcification was present in all the glands of long standing (Fig. 6).

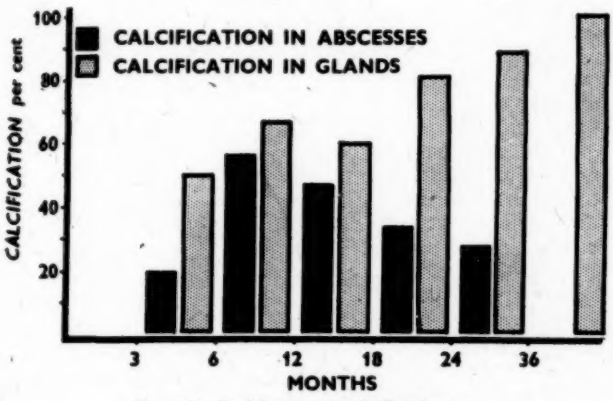

FIG. 6.—Incidence of calcification.

I would again draw attention to the importance of the site of vaccination on the arm—at any age—because if the injection be given much above the insertion of the deltoid there is an increased risk of supraclavicular adenitis and a commensurate possibility of breaking-down in this region because of its association with the cervical glands and their involvement in repeated upper respiratory infections.

There is no need to stress these complications, because we know they are all minor in character and will heal spontaneously in time. Nevertheless, they can be worrying to parents and disfiguring to the infant, even if this be only temporary. Any treatment, therefore, which will accelerate healing is worth undertaking. Local surgical treatment, excision or incision, is rarely necessary. Aspiration is ofter helpful, with isoniazid, streptomycin, or P.A.S. replacement. Ultra-violet light locally is also of value in accelerating healing. Exposure to fresh air and sunlight is probably the best treatment of all. It has been very striking how secondary infection has been absent, even in the longest-continuing sinuses.

Early Vaccination and Immunization

It is, then, well established now that newborn infants can react satisfactorily, and we have vaccinated them on the first day of life; this applies to even the less immature premature infants, for we have vaccinated a number of premature infants to determine this fact and found that they reacted well and converted promptly with the same dose as full-term infants. The smallest infant weighed 3 lb. 15 oz. (1.8 kg.), and with only 0.05 ml. of vaccine—that is, 0.0375 mg.—converted after eight weeks. There were no adverse systemic effects in any of the premature infants, but an increased incidence of adenitis makes us consider it advisable to postpone vaccination till maturity is reached, although most premature infants could safely be vaccinated and be allowed to convert before leaving the nursery—that is, at 5 lb. (2.3 kg.) or thereabouts—and in contact cases this would obviate the need for subsequent segregation.

Immunization at birth against diphtheria, whooping-cough, and tetanus, singly or combined, is being practised effectively in many centres. In my department, Dr. G. V. Feldman has, concurrently with our own studies, immunized some 1,500 newborn infants against these infections and found that an adequate response, both serologically and clinically, *can* be obtained, and that, in the main, when failure occurs it is more likely to be attributable to the vaccine than to the infant.

It has been suggested that in the administration of combined antigens there is likely to be dominance of one, to the possible detriment of another, and his experience has borne this out. The same may consequently apply to different antigens given within a short time; an interval of at least four weeks should therefore elapse between two different vaccinations, such as tuberculosis and smallpox, if the optimal effect of each is to be obtained with certainty.

It is true that there are certain differences of reaction in the newborn, particularly regarding speed and intensity, but these differences cannot, we feel, be considered sufficient to justify postponement of active prophylaxis where this is indicated (Figs. 7 and 8).

In regard to tuberculosis particularly, it is impossible to protect an infant too early. Although, as I have said, the immediate contacts can be found in a great many cases of infection in children—and the

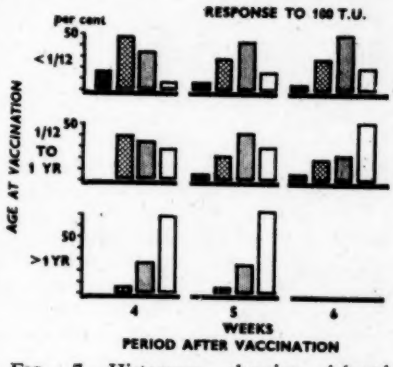

FIG. 7.—Histogram showing delayed response in newborn.

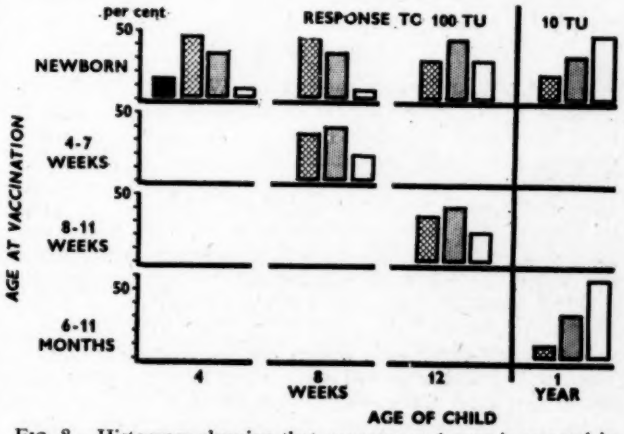

FIG. 8.—Histogram showing that response at 1 year is as good in infants vaccinated at birth as in those vaccinated after the newborn period.

Key to histograms. *Mantoux Reactions*

■ Induration <5 mm. ▨ Induration 10–15 mm.
▩ ,, 5–9 mm. □ ,, >15 mm.

younger the infant, the greater the number—in a recent study Walker (1955) found that even under 3 years of age the contact was unknown in 33% of 194 children, so that family freedom is not by any means indicative of immunity of any infant from infection. Bentley found that more than 30% of the tuberculous meningitis in his children at High Wood originated in the first two years of life, and, what is particularly striking, in 16 of the 41 infants so affected no contact could be traced.

An infant may be exposed to infection at birth or at any time thereafter, and whatever method of vaccination is used a certain minimal amount of time must elapse before any protection can be afforded. The shorter this minimal period is after birth, the greater are the chances of preventing tuberculosis. Another point in favour of vaccination in the newborn period is the ease of access to the infant while he is still immobilized, either at home or in hospital, and this is of great practical importance. If prophylactic immunization is undertaken the vaccine is brought to him: he is not dependent on his mother's taking him to the doctor or to a clinic. Another minor but not entirely irrelevant point is that at this age no pre-vaccination tuberculin test is necessary.

It may well be asked, "Will vaccination serve to provide protection in the first six months of life?" The theoretical answer should be, "No—it takes some time for the vaccine to exert its influence." Yet practical experience shows that there may after all be some value even in the early days after vaccination, for the protection should not be, and, indeed, experimentally has been shown not to be, dependent on tuberculin conversion, which is only an expression of allergy. Protection may start before conversion, and persist after reversion. The truth of this early protection is borne out by the very few infants vaccinated at birth who have contracted tuberculosis in the first six months of life. Gyllenswärd (1949) has pointed this out in Swedish infants in whom—with the more attenuated vaccine in use in that country, often not giving conversion for ten to twelve weeks—there has nevertheless been a negligible mortality in these first six months.

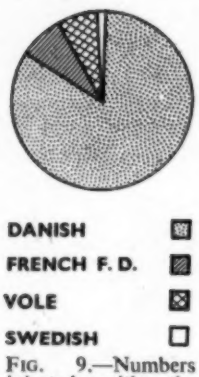

FIG. 9.—Numbers injected with the various vaccines. Danish, 5,991; French freeze-dried, 569; vole, 516; Swedish, 39.

We have used a variety of vaccines, but chiefly Danish, French, vole, and Swedish. Fig. 9 shows the relative numbers of each.

Vole Vaccine

With regard to the vole vaccine, Dr. Wells has supplied us fortnightly with this vaccine, of constant antigenicity, all from one strain, and it has the great advantage of being prepared with a definite number of bacilli per ml. instead of by weight. Using the intradermal method of vaccination, as we have throughout, this means that we have been able to control to a reasonable degree of accuracy the actual number of bacilli injected—and they have been almost 100% live bacilli. The practice hitherto has been to vaccinate by multiple puncture when using vole vaccine, but we determined to continue with our existing intradermal routine.

We started tentatively, at Dr. Wells's suggestion, with a dose of 50,000 bacilli and were more than agreeably surprised to obtain a conversion with 100 T.U. after as short an interval as eight days. And this, for newborn infants, is something worth achieving, particularly from the practical point of view in relation to segregation. Subsequently we found the Danish vaccine did just as well with regard to the rapidity of conversion.

However, some three to six months later it became evident that this dose of vole vaccine must be reduced, because, although the local lesion was not excessive—indeed, no more than B.C.G. produced—and there were no systemic upsets, the axillary glands overflowed in too many.

Reduction of dose proceeded by gradation until we reached the phenomenally low figure of 1,250 bacilli, with which a higher proportion of non-conversions at four weeks became evident than in B.C.G. vaccinations (41% positive with vole against 97% with B.C.G.), though of course they all converted later (Figs. 10 and 11).

There has been only one case with an axillary abscess at the low dosage, but even this one shows that the margin between minimal effective dose and that producing undesirable side-effects is narrow. However, as Wells and Wylie (1954) had recorded that 1,000 times the optimal dose of vole vaccine has been given intradermally to several people without any harm, save the unpleasantness of excess local reaction, we did not anticipate any systemic disturbances, and, indeed, none were encountered. So far, in the yearly follow-up there have been no reversions after vole vaccination with doses of 25,000 bacilli or more; indeed, the tuberculin response with 1 T.U. has been better than with B.C.G., and this may prove to be an important factor (Fig. 12).

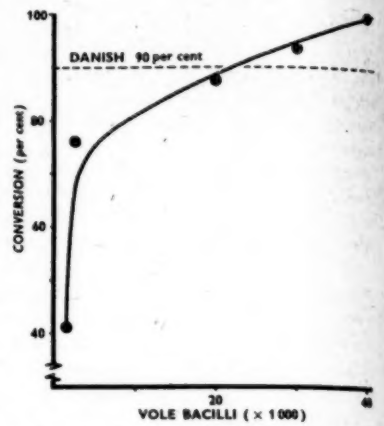

FIG. 10.—Reaction to 100 T.U. at four weeks. (Conversion.)

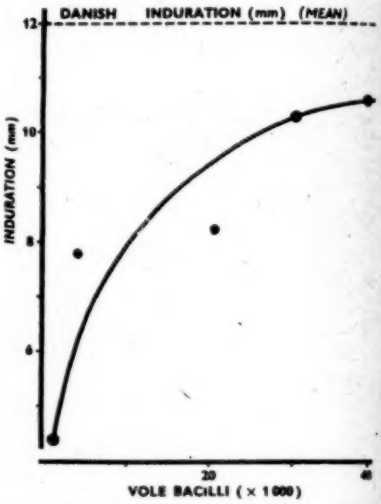

FIG. 11.—Reaction to 100 T.U. at four weeks. (Induration.)

After discussion with Dr. Wells and Dr. Vollum we then decided to try the effect of a preliminary injection of dead bacilli followed after a week by the live vaccine to see whether this would diminish the number and size of the glandular reactions without affecting conversion. Practical difficulties, however, led to the abandoning of this technique; firstly because some of the mothers did not return with their infants after the initial injection of dead bacilli only, and, despite having been told that a second injection was necessary before the vaccination

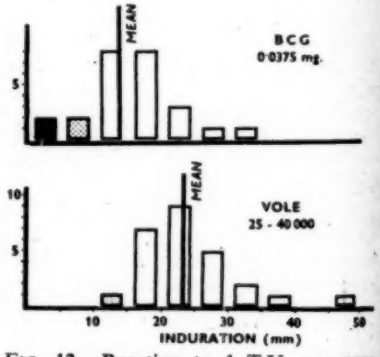

FIG. 12.—Reaction to 1 T.U. one year after vaccination.

could be considered complete, may well have considered their infants protected and consequently relaxed essential hygienic precautions. Secondly, this method obviously involved an increase in the time elapsing before adequate protection could be given.

We next mixed live and killed bacilli in known proportions—1,250 live and 12,500 killed—at a single injection to confirm or refute Palmer's suggestion that a mixture of live and dead bacilli was better than 100% live bacilli. We found that conversion was better with the mixture, thus agreeing with Palmer, and opening the way for further interesting study of varying combinations (Fig. 13).

This 1,250 bacilli level is a remarkable reduction from the accepted figure for B.C.G., and this is directly due to the greatly increased potency of vole vaccine. It is quite conceivable that we shall find that even half this dose will suffice.

Wells and Wylie recorded lupoid reactions at the vaccination site in 3.3% of their cases. We have had no such cases so far. They found, however, as compensation, that the incidence of tuberculosis in 2,500 vaccinated persons was 0.085% compared with 2.35% in their controls. Only seven cases of lupus following B.C.G. have been recorded so far; we have seen none. Frew and his colleagues (1955) reported that the lupoid reactions after vole vaccination healed well.

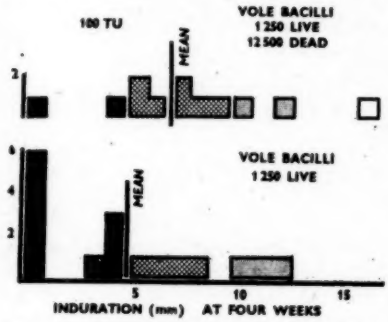

FIG. 13.—Results with mixed live and killed bacilli compared with those from 100% live bacilli.

Wells also found a higher and longer-lasting sensitivity than that produced by B.C.G., and, experimentally, he found a greater resistance to challenge infection in guinea-pigs—and this resistance outlasted the tuberculin sensitivity.

At present it is too early to define clearly the future position of vole vaccine in infants. It has certain advantages—uniformity, viability, and known number of organisms—and certain disadvantages resulting from its highly antigenic properties, which make the margin between complication-producing dose and minimal effective dose rather narrow. With minimal doses the conversion time is prolonged, and this is certainly a disadvantage in contact infants requiring segregation.

A possibility to be considered is the deliberate attenuation of the bacilli, as in the case of B.C.G., by growing them on bile-salt media as has been suggested by Cronin (1954); but this would relegate vole vaccine to a mere alternative to B.C.G. without any of the advantages which it may well finally prove to have, unless it is possible to produce a limited degree of attenuation, approximately half-way between its present potency and that of B.C.G.

We are following up closely those infants whom we have vaccinated with vole bacilli, and if, with the low dose we have used most recently, or an even lower one, complications are few and allergy reasonably maintained for as long as or longer than that following B.C.G. we shall certainly consider recommending its further use.

Results from Various Vaccines

The differing antigenicity of various vaccines has produced a striking difference in the results (Fig. 14). Stein and Aronson (1953) noted this, for they found that their 4% of vaccinated subjects who had radiological evidence of pulmonary tuberculosis had been those vaccinated with a low-antigenicity vaccine. Rosenthal (1952) found that he had to wait 58 days to get conversion with a freeze-dried vaccine, as compared with 28 days when fresh B.C.G. was used; this is a significant time difference if segregation is considered.

This variation in vaccines may depend on the parent strain, cultural differences (including date of collection), and the percentage of live to dead organisms. Also, of course, on the method of keeping (length of time, temperature, and exposure to light), which will affect the percentage of living organisms. Birkhaug investigated the effect of time and temperature on B.C.G. and found that the vaccine lost 50% of its living population in one week at 20° C. and nearly 100% in three weeks, and nearly 100% after one week at 37.5° C.; these findings were confirmed by the diminishing vaccination lesions and post-vaccination Mantoux reactions and by reduced resistance to challenge infection in guinea-pigs.

Edwards and Gelting (1950) on the other hand, found little alteration in allergy after nine weeks at temperatures up to 20° C. and at room temperature after a month, which shows the greater importance of challenge infections than allergy and establishes a correlation between the percentage of living organisms and protection, which was stressed by Dubos and his colleagues, who concluded from their studies that the effect of the vaccine was dependent on the multiplication of the organisms *in vivo* and that live bacilli were therefore essential. Edwards and Gelting, however, wisely made two reservations in drawing their conclusions. Firstly, that they had used a potent vaccine—and their results could hold good only for similar vaccines; and, secondly, that their post-vaccination tuberculin reactions were at ten weeks, and subsequent testing might disclose major differences (Figs. 15, 16, and 17).

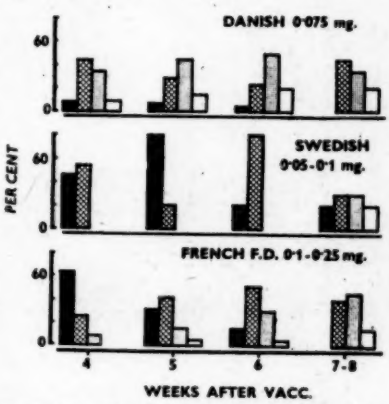

FIG. 14.—Reaction to 100 T.U. after various vaccines.

Anyone working with such a variable as a tuberculosis vaccine can draw conclusions on the efficacy only of the particular vaccine he is using, and the variations encountered are responsible for the sometimes widely different results published from different centres. For example, Dubos claims that *in vivo* multiplication of the organisms is an important part of the total reaction. Bloch (1954), on the other hand, holds that so long as there are live organisms their multiplication is not essential, and that even resting bacilli can elaborate the products necessary for immunization; the Italians hold that live organisms are not necessary at all.

For the past year we have used a special half-strength vaccine (0.375 mg./ml.) which Professor Heaf kindly arranged to be sent to us from Copenhagen. This allows of more accurate dosage. It will be seen from the mean of the responses that there is virtually no significant difference between any of them, but technically the third is the easiest and most accurate. It is not easy to give 0.05 ml. accurately to an active newborn infant (Fig. 18).

We have used O.T. and not P.P.D., and have used comparable batches of O.T. in the same way that we have with the vaccines.

After the work of Magnusson and Lithander (1949) with B.C.G. tuberculin, in which they reported that the Mantoux conversion occurred appreciably earlier in newborn vaccinated infants with this tuberculin than with ordinary old tuberculin, we tried it for a short time. Magnusson kindly sent us a supply from Stockholm, but we could obtain no

quicker conversions than with O.T., and this, I think, was probably due to the fact that his tuberculin was made from Swedish B.C.G. and therefore, although comparatively weak, was homologous with the vaccine he used, whereas we were using Danish B.C.G. I think there might well be a difference

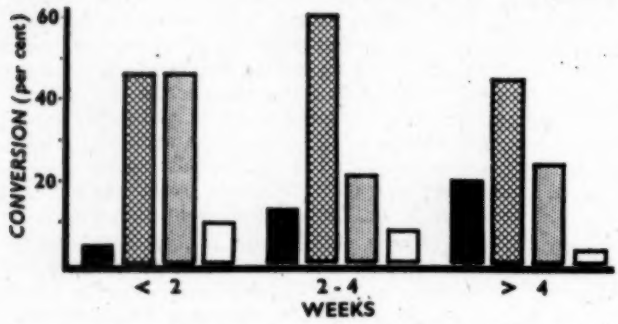

FIG. 15.—Histogram showing effect of storage (refrigerated).

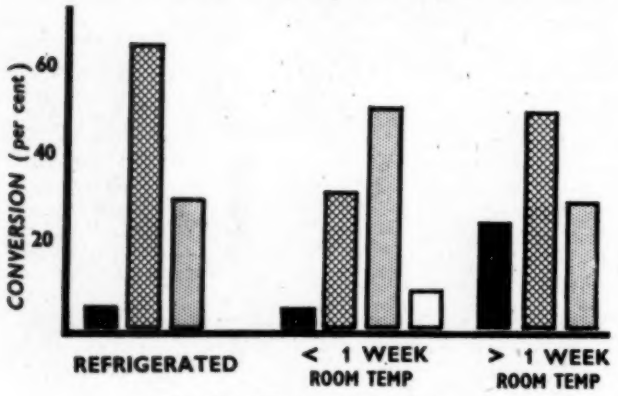

FIG. 16.—Effect of temperature.

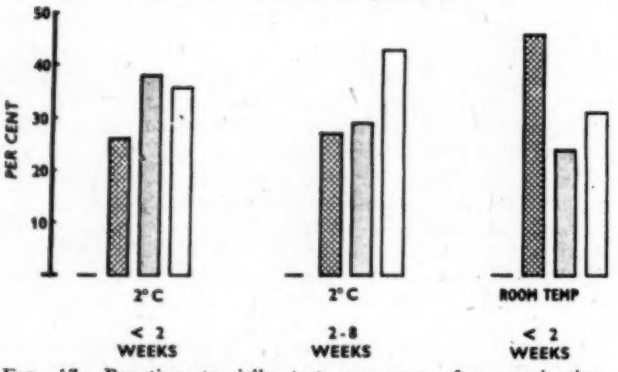

FIG. 17.—Reaction to jelly test one year after vaccination. (Danish, 0.0375 mg.)

if we could use vole tuberculin, which would undoubtedly be more potent, but there are technical difficulties in its preparation.

Palmer and Edwards (1955) showed that homologous tuberculin produces a larger reaction than heterologous and that this might be useful in differentiating between specific and non-specific reactions; for example, if the reaction to avian tuberculin was as great as that to human O.T. a non-specific reaction would be the likely explanation.

Freeze-dried Vaccines

Freeze-dried vaccine offers so many possible practical advantages that its use must be seriously considered. The longevity of the vaccine, the ease of transport, and the freedom from temperature control are all in its favour. Its disadvantages at present are the varying quantity of living organisms, its generally more marked attenuation, and the difficulty of overcoming the clumping which occurs: even solutions which are clear to the naked eye will be found to show marked clumping under the microscope, so that accurate dose estimation is almost impossible. Such vaccines will certainly provide adequate local lesions and lead to Mantoux conversions—though on an attenuated scale—and the tendency to reversion is greater than with fresh vaccine. By way of increasing the difficulty, the complications, which might be expected to be fewer, are not; for some infants get too many, some too few, bacilli, owing to the clumping. When the clumping problem is overcome there will be a much wider scope for freeze-dried preparations.

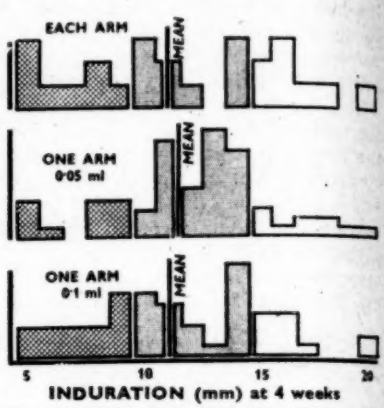

FIG. 18.—Mantoux 100 T.U. Newborn (Danish 0.0375 mg.)

We have used the dried vaccine prepared at the Pasteur Institute, and, most recently, a product made in this country which is suspended in dextran before freeze-drying. Our results with the French vaccine have been comparable with those we obtained with the fresh Swedish vaccine—that is to say, slower conversions and lower allergy—which are both disadvantages in the newborn period. On the British preparation it is too early yet to make any pronouncement, but our results so far show it to be comparable with Danish B.C.G.—at least so far as the speed and intensity of allergy development and the appearance of the local lesion—but we do not yet know how long its effects will last or whether it will enable us to reduce still further the incidence of glandular reaction. It certainly promises well.

There is certainly a decline in mortality from tuberculosis. Fig. 19 shows that the mortality in infants under 1 year has not fallen a great deal. However, the interesting

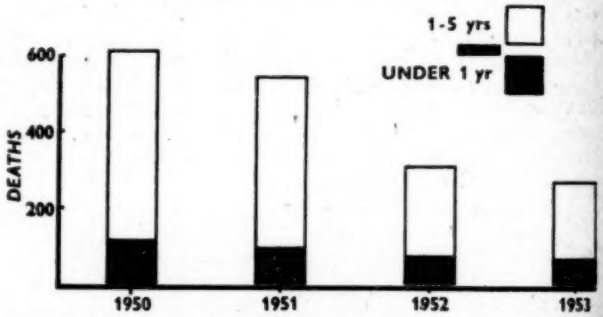

FIG. 19.—Deaths from tuberculosis under the age of 5 years. (England and Wales.)

fact is that the incidence remains high, and though the death rate (overall) dropped by 59% between 1948 and 1953 the notifications fell by only 7%. The risk of exposure therefore persists.

Certain practical problems have arisen and must be dealt with carefully if the principle of early vaccination is not to fall into disrepute.

Precautionary Measures

After successful vaccination a card should always be given to the mother stating that the infant has been vaccinated and that the Mantoux test was positive in 10 or 100 T.U., as the case might be, on the date given. This card should always accompany the infant (and, later, the child) to hospital. Surgeons are apt to be misled by swellings in the axillae or groins, particularly as by the time these appear the vaccination

has been forgotten if the infants have not been attending a follow-up clinic. Physicians too, viewing shadows and opacities in the thorax or investigating a child with a cough, should know of a preceding vaccination, for such shadows will surely be non-tuberculous, but B.C.G. will not prevent a child from having a cough.

Furthermore, the family doctor and welfare clinic should always be informed of the vaccination, so that due care may be exercised when other prophylactic immunizations are undertaken; for the arm used for B.C.G. should be "rested" for at least six months, whereafter lighting up of the vaccination site or regional nodes is unlikely. We have for some time now used the right arm routinely for our vaccinations, except in those contact infants in whom we divided the dose and gave half into each arm. We have thus left one arm free for any other prophylactic or therapeutic procedure. Personally, even if a double dose is to be given, I prefer to give it at a single site even if that should increase the risk of adenitis, for this allows one arm to be completely free.

Conclusions

Finally, what conclusions can we draw from our studies? They are:

That infants are at risk and that this cannot be prevented. That vaccination at birth is safe, practicable, and effective, though it does not obviate the need for segregation and for general hygiene and education in hygiene. That it would appear that vaccination is effective in protecting throughout the danger period of infancy, though we do not know whether revaccination may not be necessary at 10–12 years; this may well depend on any exposures in the intervening years. That, of all the vaccines we have used, quickest conversion is afforded by the standard Danish B.C.G. That a half-strength vaccine—that is, 0.375 mg. per ml.—is preferable for this work in infants, as it allows of more accurate dosage. That the complications are mainly directly proportional to the antigenic potency of the vaccine and to the dose given. That until the tuberculous antigen is isolated, vaccination with live attenuated bacilli offers a sound means of protection, and, because of the urgent need of this protection from the earliest possible moment, vaccination may most profitably be undertaken in the newborn period despite the slightly increased risk of glandular complication at this age, provided the vaccine is given in accurate dosage, by an experienced person.

That when potent freeze-dried vaccine is available generally the problem of "shortevity" and temperature control will no longer cause difficulty in distribution. A freeze-dried vaccine, free from clumping when dissolved, and containing a known number of evenly distributed and living bacilli, allowing of accurate controlled dosage, will be a great step forward.

That in view of the need for careful follow-up and the difficulty of getting sufficient trained personnel it would not be practicable to carry out mass vaccination in the newborn at present even if that were desirable. Nevertheless, where facilities exist—that is, in maternity hospitals and where there is experienced paediatric supervision—we believe that vaccination in the newborn period offers a very real contribution to the protection of infants against tuberculosis, and we consider that it might with advantage become an accepted part of the "care of the newborn" in maternity hospitals. But, apart from such hospitals, we think that it should at present be reserved for infants who are known to come from, or be going to, tuberculous households, and in these it should be a routine procedure as soon after birth as possible—that is, during the first week of life. Many such infants are, of course, born at home or in district maternity homes, and not every district has a paediatrician, but there are maternity and child welfare doctors in all areas, and one or more of these from each area could be trained to undertake this special work without its adding greatly to his or her existing clinical commitments, and so all infants at known risk could in fact be satisfactorily vaccinated.

I would conclude with the warning that with the changing pattern of tuberculosis and the rapidity of introduction of new antituberculous chemotherapeutics our future programme may well differ significantly from that which I have outlined.

I am greatly indebted to my obstetric colleagues for their co-operation and to Professor Frederick Heaf and Dr. A. Q. Wells for their practical help and advice. All the illustrations were prepared by the Department of Medical Illustration of the United Manchester Hospitals under the direction of Dr. Ollerenshaw, to whom I tender my thanks. The collation of all the details from the clinic records has been undertaken by Dr. Margaret Griffiths, who has had constant charge of the running of the clinic since its inception. I am particularly grateful to her for this work and for all the help she has afforded me in the preparation of these lectures.

References

Aronson, J. D., and Aronson, C. F. (1952). *J. Amer. med. Ass.*, **149**, 334.
Bentley, F. J., Grzybowski, S., and Benjamin, B. (1954). *Tuberculosis in Childhood and Adolescence*. N.A.P.T., London.
Biering-Sorensen, K. (1953). *Acta paediat. (Uppsala)*, **42**, 387.
Birkhaug, K. (1953). *Amer. Rev. Tuberc.*, **68**, 188.
Bloch, H. (1954). *Modern Problems in Pediatrics*, p. 542. Karger, New York.
—— Widelock, D., and Peizer, L. R. (1953). *Amer. Rev. Tuberc.*, **68**, 734.
British Medical Journal, 1955, **1**, 1076.
Cronin, M. J. I. (1954). *J. comp. Path.*, **64**, 234.
Djourichitch, P., Nechcovitch, P., and Radoytchitch, V. (1953). *Presse méd.*, **61**, 82.
Dubos, R. J. (1953). *Amer. Rev. Tuberc.*, **67**, 874.
—— Pierce, Cynthia H., and Schaefer, W. B. (1953). *J. exp. Med.*, **97**, 207.
Edwards, Lydia B., and Gelting, Anna S. (1950). *Bull. Wld Hlth Org.*, **3**, 1-186.
Enell, H. (1955). *Acta paediat. (Uppsala)*, **44**, Suppl. 101.
Fisher, M. W. (1954). *Proc. Soc. exp. Biol. (N.Y.)*, **85**, 538.
Frew, H. W. O., Davidson, J. R., and Reid, J. T. W. (1955). *British Medical Journal*, **1**, 133.
Gaisford, W., and Griffiths, Margaret (1954). *Tubercle*, **35**, 7.
Gyllenswärd, C. (1949). *Acta paediat. (Uppsala)*, **38**, 215.
Hagberg, E. (1954). Ibid., **43**, 394.
Heaf, F. R. G. (1955). *Lancet*, **1**, 315.
Hesselman, B. E. (1951). *Acta paediat. (Uppsala)*, **40**, 366.
Hewell, Barbara, and McClellan, M. (1954). *Amer. Rev. Tuberc.*, **70**, 1064.
Iland, C. N. (1953). *Lancet*, **2**, 277.
Jachnis, B. L. (1947). *Probl. Tuberk.*, **3**, 26.
Joint Tuberculosis Council (1955). *The Changing Character of Tuberculosis*.
Jorup, S. (1946). *Svenska LäkT.*, **43**, 149.
Karlson, A. G., and Ikemi, Y. (1954). *Proc. Mayo Clin.*, **29**, 119.
Kringelbach, J. (1954). *Acta paediat. (Uppsala)*, **43**, 304.
Lancet, 1955, **1**, 756.
Lesné, E., Cayla Roche, and Allard (1949). *Sem. Hôp. Paris*, **25**, 2083.
Lincoln, Edith M. (1954). *Amer. Rev. Tuberc.*, **69**, 682.
Lurie, M. B. (1942). *J. exp. Med.*, **75**, 247.
Maclouf, A. C., and Fichez, L. F. (1952). *Rev. Tuberc. (Paris)*, **16**, 1016.
Magnusson, J. H., and Lithander, A. (1949). *Pediatrics*, **3**, 429.
Marquézy, R. A., Bach, C., and Clermont, J. P. (1953). *Presse méd.*, **61**, 1569.
Meyer, S. N., and Palmer, C. E. (1954). *Amer. Rev. Tuberc.*, **69**, 383.
Mitchell, G. F., and Willis, H. S. (1944). Ibid., **50**, 316.
Nègre, L. (1954). *Ann. Inst. Pasteur*, **86**, 1.
Palmer, C. E., and Edwards, Phyllis Q. (1955). *Bull. Wld Hlth Org.*, **12**, 85.
—— Nash, F. A., and Nyboe, J. (1954). *Lancet*, **2**, 1274.
Rich, A. R. (1951). *Pathogenesis of Tuberculosis*, 2nd ed. Thomas, Springfield, U.S.A.
Rollof, S. I., Lagercrantz, R., and Lind, J. (1954). *Acta paediat. (Uppsala)*, Suppl. 100, p. 179.
Rosemberg, J. (1954). *Tuberkulosearzt*, **8**, 38.
Rosenthal, S. R. (1952). *Acta tuberc. scand.*, **26**, 106.
Salvioli, G. (1953). *Arch. Dis. Childh.*, **28**, 36.
Siebenmann, C. O. (1951). *J. Immunol.*, **67**, 137.
Smellie, J. M. (1954). *Lancet*, **2**, 1091.
Söderling, B. (1939). *Acta paediat. (Uppsala)*, **23**, Suppl. 2.
Stein, S. C., and Aronson, J. D. (1953). *Amer. Rev. Tuberc.*, **68**, 695.
Ström, L. (1950). *Acta paediat. (Uppsala)*, **39**, 453.
—— and Widström, G. (1951). Ibid., **40**, 213.
Suter, E. (1953). *J. exp. Med.*, **97**, 235.
Todd, R. M. (1955). *Lancet*, **1**, 794.
Trail, R. R. (1955). Personal communication.
Verschner, O. von (1950). Cited by C. Stern, *Principles of Human Genetics*, p. 481. Freeman, San Francisco, U.S.A.
Walker, C. H. M. (1955). *Lancet*, **1**, 218.
Wandelt, Mabel A. (1954). *Amer. Rev. Tuberc.*, **70**, 490.
Wells, A. Q. (1937). *Lancet*, **1**, 1221.
—— and Wylie, J. A. H. (1954). *Brit. med. Bull.*, **10**, 96.
Wilson, May G., and Schweitzer, M. (1954). *Circulation*, **10**, 699.
Zeidberg, L. D., Dillon, Ann, and Gass, R. S. (1954). *Amer. Rev. Tuberc.*, **70**, 1009.

CLINICAL TRIALS OF *p*-(DI-2-CHLOROETHYLAMINO)-PHENYLBUTYRIC ACID (CB 1348) IN MALIGNANT LYMPHOMA

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Everett, Roberts, and Ross (1953) synthesized a series of water-soluble aromatic nitrogen mustards, one of which, *p*-(di-2-chloroethylamino)-phenylbutyric acid (CB 1348), was found to be a powerful inhibitor of the transplanted Walker rat tumour 256 (Haddow, 1952) and was submitted for clinical trial.

Ninety-three patients suffering from advanced carcinoma and from lymphomas have been treated with CB 1348 since September, 1952. This report concerns only the cases of malignant lymphoma, of which there were 76. Fourteen of these have been omitted from the report because the diagnosis was in doubt, because of inadequate follow-up, or because incomplete treatment was given. The 62 remaining cases include 23 of Hodgkin's disease, 20 of lymphocytic lymphoma (including eight cases of chronic lymphocytic leukaemia), 11 of reticulum-cell sarcoma, 6 of follicular lymphoma, and 1 each of generalized exfoliative erythrodermia and mycosis fungoides.

Administration, Dosage, and Side-effects

Administration was usually by mouth, but a few patients received the sodium salt intravenously, either alone or in addition to oral therapy. The sodium salt was given intraperitoneally to one patient with disseminated reticulum-cell sarcoma and ascites.

With few exceptions the oral dose ranged from 2 to 20 mg. a day (0.03–0.34 mg. per kg. of body weight). In most cases it was either 0.1 or 0.2 mg. per kg. daily (6 or 12 mg. for a patient weighing approximately 10 stone—63.5 kg.). A course of treatment usually lasted three to six weeks, but CB 1348 was given daily for 8 to 16 weeks on thirteen occasions and for 6 to 12 months on three. Eighteen patients had more than one course of treatment; 15 were given two courses at intervals of from 3 to 27 months; two had three courses; and one (Case 4) had six.

Treatment with CB 1348 was stopped when satisfactory improvement had been obtained. In some cases a course had to be terminated because of neutropenia or thrombocytopenia. If there was no response treatment was usually continued for six weeks before concluding that the patient was resistant to the drug. Prolonged treatment was given when improvement was progressive and the blood picture offered no contraindication. Twenty-five patients received more than 0.5 g. of CB 1348, the largest total dose being in Case M. W. (Table III), who was given 1.93 g. in the course of 12 months' continuous treatment.

Four patients complained of epigastric or retrosternal burning pain, and a patient with a duodenal ulcer developed recurrence of dyspeptic symptoms after taking 6 mg. of CB 1348 daily for one month. This patient later took the drug for two months without ill effect.

Four patients with Hodgkin's disease were given three- or four-day courses to a total dose of 120 mg. (1.65–2 mg. per kg.). All experienced nausea and two vomited once. This method of treatment has no advantage and has been discontinued.

For intravenous use, the sodium salt was freshly made up in isotonic sodium bicarbonate. Single doses varied from 10 to 20 mg. In one case single doses of 70 mg. were given. The injections were always well tolerated, and did not damage the veins or cause vomiting. However, doses of 100 mg. were given in some cases of advanced carcinoma not included in this report, and were usually followed 6–18 hours later by vomiting. Intraperitoneal injection was well tolerated.

Results

The results are summarized in Table I. By "benefit" we mean improvement of real value to the patient, so that as a result of treatment he can return to something approaching a normal life for at least six months. Improvement of shorter duration, however striking, is classed only as "some effect."

TABLE I.—*Results of Treatment with CB 1348 in 62 Cases of Lymphoma*

Diagnosis	No. of Patients	Benefit	Some Effect	No Effect
Hodgkin's disease	23	4	14	5
Reticulum-cell sarcoma	11	0	6	5
Lymphocytic lymphoma, subleukaemic	12	7	3	2
Chronic lymphocytic leukaemia	8	4	1	3
Follicular lymphoma	6	5	1	0
Mycosis fungoides	1	0	0	1
Exfoliative erythrodermia	1	0	1	0
Total	62	20	26	16

Hodgkin's Disease

Twenty-one patients had been ill for six months to six years and had already received specific treatment. Most of them had had deep *x*-ray therapy and a few had had di-(2-chloroethyl)-methylamine (HN_2, mustine), di-2-chloroethyl-β-naphthylamine (CB 1048, formerly R 48), or triethylene melamine (T.E.M.). Two had not been treated previously. One had generalized disease of acute onset. In the other the disease was apparently confined to a single mass of mediastinal nodes.

Four patients derived real benefit (Cases 1–4). Fourteen responded in some degree, showing favourable effects on fever, sweats, pruritus, enlarged lymph nodes, spleen, and haemoglobin level. However, these effects were short-lived and of little clinical importance. In five patients CB 1348 failed to influence the condition at all.

Case 1.—A woman of 63 was admitted with generalized Hodgkin's disease of acute onset in April, 1953. She was given CB 1348, 10 mg. daily (0.2 mg. per kg.) for 38 days. Within the first 14 days of receiving the drug, fever and sweats abated, skin rash faded, pruritus was relieved. Rapid regression of enlarged ulcerated tonsils, cervical, axillary, and inguinal nodes, and spleen followed. The Hb level rose

by 33% (4.9 g. per 100 ml.), reaching 108% (16 g. per 100 ml.) in six months. The spleen began to enlarge 15 months after treatment was stopped, but the patient remained well for another two months. Her condition then deteriorated; the Hb level fell 20% (2.96 g. per 100 ml.), the platelet count dropped from above 200,000 to below 100,000 per c.mm., and the neutrophil count fell from 11,000 to 3,100 per c.mm. In spite of this a second course of CB 1348, 10 mg. daily for 22 days, was given in January, 1955. She remained weak and febrile, and the fall in haemoglobin level and enlargement of lymph nodes, liver, and spleen continued. No further neutropenia or thrombocytopenia ensued and treatment was abandoned because it was ineffective. Cortisone was given without benefit. She died on February 28.

Case 2.—A boy of 14 was found to have enlargement of cervical and axillary nodes and splenomegaly in December, 1952. A diagnosis of Hodgkin's disease was made by biopsy of a lymph node. Radiotherapy caused the nodes and spleen to regress, but one month later he experienced the first cycle of severe remittent fever. Treatment with CB 1348 was begun in May, 1953, with doses of 6–10 mg. daily (maximum 0.2 mg. per kg.) for seven weeks (total 420 mg.). The febrile attacks were favourably modified; he gained weight and was able to return to school for six months. In February, 1954, the febrile attacks again became severe. Further treatment with CB 1348 was effective for only a few weeks; the fever became continuous and he died in August, 1954.

Case 3.—A man of 33 had had Hodgkin's disease for five years, for which he had been given radiotherapy and T.E.M. In January, 1954, he was febrile, anaemic, anoretic, and had lost weight. He was given CB 1348, 10 mg. daily for 14 days (0.13 mg. per kg.). Fever abated, he gained 43 lb. (19.5 kg.) in weight, the enlarged liver and spleen regressed, and the Hb level rose 39% (5.8 g. per 100 ml.). The remission lasted almost a year, a previous remission after treatment with T.E.M. having lasted only three months. A second course of CB 1348, 10 mg. daily for three weeks, was given in December, 1954, because of recurrence of sweating, fever, anorexia, and loss of weight. The response, though satisfactory, was short-lived, and a third course at the same dosage was given in April, 1955, again with relief of symptoms. In October, 1955, he was free from symptoms.

Case 4.—A woman of 44 had had Hodgkin's disease for six years. She had been treated with deep *x*-ray therapy and T.E.M. In December, 1953, she had fever, anorexia, and hepatosplenomegaly. Since then she has had six courses of CB 1348, 10 mg. daily (0.18 mg. per kg.)—for three weeks in the first two courses, for five to seven weeks in the last four. Each time fever subsided, weight increased, and the spleen regressed. The remission after the first course lasted four months; that after the sixth lasted 6 weeks. The response to CB 1348 was better than to T.E.M.

The results of treatment in generalized Hodgkin's disease are disappointing, because so few patients secured worthwhile benefit. In these few patients the results were striking, but we cannot recognize any special feature common to the successfully treated patients that distinguishes them from the larger number who responded less well or not at all. In eight cases comparison can be made between the efficacy of CB 1348 and that of previous and subsequent chemotherapy. In two cases CB 1348 gave a better response than T.E.M.; in two T.E.M. seemed better, but in one of these CB 1348 was given late in the disease. In one case the response to CB 1348 was similar to that previously obtained with R 48 (CB 1048), mustine, and T.E.M. In another, CB 1348 and T.E.M. were equally ineffective, but a good response was obtained to radiotherapy. In one case the temporary response to actinomycin C was similar to that previously obtained with CB 1348. In another case the response to a combination of CB 1348 and cortisone was better than to either alone. Later a course of T.E.M. and cortisone had a similar effect.

Lymphocytic Lymphoma

1. Chronic Lymphocytic Leukaemia

All eight patients had enlarged spleens and livers. Only two had received previous treatment other than blood transfusions. Anaemia was severe in five cases (Hb level below 45%—6.3 g. per 100 ml.) and moderate in three (Hb level 67% to 79%—10 to 11.7 g. per 100 ml.). The results are summarized in Table II.

In four of the five severely anaemic patients frank haemolysis was demonstrated. Response to treatment with CB 1348 was good in one of these (Case 5) and in the severely anaemic patient without evidence of haemolysis (Case 6). The three remaining patients with evidence of haemolysis did not respond to CB 1348. In two the direct antiglobulin test was positive, and one of these patients responded temporarily to cortisone.

Case 5.—A woman of 77 was found to have chronic lymphocytic leukaemia. The spleen was grossly enlarged. A transfusion of 3 pints (1.7 litres) of blood did not raise the haemoglobin level or prevent its fall. The direct antiglobulin test was negative. The bone marrow showed considerable erythropoietic activity and many of the lymphocytes in the blood were early forms. In August, 1953, she was given CB 1348, 6 mg. daily (0.1 mg. per kg.) for 23 days (total 138 mg.), followed 11 days later by a further 70 mg. in 14 days. During treatment a transfusion of 4 pints (2.3 litres) of blood raised the haemoglobin level from 39% to 54% (5.8 to 8 g. per 100 ml.) and a further rise to 82% (12.2 g. per 100 ml.) followed in the next 10 weeks. The spleen regressed, the leucocyte count fell to normal, although relative lymphocytosis persisted, and the platelet count rose from 90,000 per c.mm. before treatment to 300,000 three months later. Three short courses of 2 mg. of CB 1348 daily lasting two to four weeks were given during the next four months. She remained well for one year, but subsequently failed to respond to CB 1348, to irradiation of the spleen, or to cortisone.

Case 6.—A man of 76, with no demonstrable haemolysis, obtained a good response after treatment with CB 1348, 6 mg. daily (0.1 mg. per kg.) for 20 days. The platelet count remained below 100,000 per c.mm. for seven weeks, but subsequently rose above this level. The Hb rose from 42 to 84% (6.2 to 12.4 g. per 100 ml.) in three months. Eleven months later he had relapsed.

Two of the three moderately anaemic patients, none of whom had received previous treatment, responded well to CB 1348. One was thrombocytopenic before treatment. The third had few symptoms and his condition was substantially unchanged by treatment (W. F. Table II).

Case 7.—A woman of 54 bruised easily and was found to have moderate enlargement of the liver and spleen, a positive capillary fragility test, and a platelet count of 45,000 per c.mm. She was given CB 1348, 10 mg. daily (0.2 mg. per kg.) for 27 days (total 5.4 mg. per kg.). The spleen regressed for four months after the treatment, but remained just palpable. The liver became impalpable. The Hb level rose 15% (2.22 g. per 100 ml.) in six months. The platelet count fell during treatment and for two weeks afterwards, but rose quickly thereafter. It remained between 100,000 and 200,000 per c.mm. for 16 months. Two months later the platelet count was 35,000 per c.mm. but again rose after treatment with cortisone and CB 1348. She is well 2¼ years from the time of diagnosis.

In the following case, CB 1348 was given continuously over a period of seven months.

Case 8.—A man of 62 was found to have chronic lymphocytic leukaemia during investigations for bronchiectasis. During seven months of treatment with CB 1348 (4–10 mg. daily—0.05–0.14 mg. per kg.; total 1.3 g. in 28 weeks) regression of lymph nodes, spleen, and liver took place, he gained 20 lb. (9 kg.) in weight, and the Hb level rose 20%. The leucocyte count fell from 160,000 to 14,000

TABLE II.—*Eight Patients with Lymphocytic Leukaemia. Results of Treatment with CB 1348*

Case No.	Sex	Age	Condition Before Treatment					Dose of CB 1348				Condition After Treatment			Remarks
			Hb* %	Direct Antiglobulin Test	Evidence of Haemolysis	Platelets per c.mm.	Splenic Enlargement	Max. (mg./day)	Max. (mg./kg. per day)	Duration (Weeks)	Total (mg.)	Effect on Spleen	Effect on Hb %	Effect on Platelets (per c.mm.)	
5	F	77	37	−	+	90,000	Gross	6 2	0·1 0·03	6 11	208 126	Moderate regression	Reached 82% in 10 weeks	100,000–300,000 in 10 counts during 1 year	Good remission 1 year. No subsequent response to CB 1348 or cortisone
6	M	76	42	−	−	56,000–90,000	,,	6	0·1	3	120	Marked regression	Reached 84% in 17 weeks	90,000–150,000 in 7 counts during 4 months	Good remission 1 year
R. E.	F	71	40	+	+	70,000	Moderate	4	0·1	16	112	Moderate regression	Reached 68% in 10 weeks	Nil	Temporary response to cortisone given concurrently with CB 1348. Fatal haemolytic crisis
W. G.	M	70	39	+	+	320,000	Slight	8	0·12	12	566	Nil	Nil	,,	Cortisone and splenectomy also without effect
M. G.	M	64	40	−	+	180,000	Gross	6	0·1	6	214	,,	,,	Fell to 58,000	No benefit
7	F	54	79	−	−	45,000	Moderate	10	0·2	4	270	Marked regression	Reached 94% in 6 months	Fell to 12,000: subsequent rise to 200,000	Remission maintained 18 months; then recurrence of thrombocytopenia
8	M	62	67	−	−	450,000	,,	10	0·14	28	1,314	,, ,,	Reached 87% in 6 months	Fell to 250,000	Remission in progress 11 months
W. F.	M	59	72	−	−	70,000	Gross	6	0·1	6	162	Slight regression	Nil	Nil	Unchanged. Stationary 13 months later

* 100% Hb = 14·8 g. per 100 ml.

TABLE III.—*Twelve Patients with Lymphocytic Lymphoma. Results of Treatment with CB 1348*

Case	Sex	Age	Dose of CB 1348			Duration of Treatment (Weeks)	Clinical State Before Treatment	First Evidence of Benefit Weeks After First Dose	Maximal Improvement Attained. Weeks After First Dose	Duration of Improvement from Start of Treatment (Months)	Comments
			Daily (mg.)	Max. Daily (mg./kg.)	Total (mg.)						
H. M.	F	30	6–10	0·17	418	12	Incapacitated. Hb 82%	3	11	27 Continues	Resumed household duties. Spleen and liver became impalpable. Nodes regressed. Hb rose 20%
T. F.	M	58	6–20	0·3	792	12	Incapacitated by abdominal pain. Not anaemic	2	12	20 Continues	Pain associated with abdominal nodes improved after 2 weeks. Complete regression nodes all areas. Recurrence one node 1 year later. No further treatment. Working
M. W.	M	64	2–6	0·1	1,930	52	Seriously ill. Hb 85%	4	36	12	Further radiotherapy precluded by skin condition. Resumed work 3 months after treatment. Liver and spleen impalpable after 9 weeks. Nodes continued to regress for 9 months. Recurrence 14 months. Died septicaemia 15 months
S. W.	M	57	2–10	0·15	596	15	Incapacitated. Hb 63%	3	6–10	7 Continues	Much previous radiotherapy. Resumed work 6 weeks after first dose. Three months later spleen, liver, nodes had regressed completely. Hb rose 30%
R. W.	M	61	10	0·15	540	8	Seriously ill. Not anaemic	2	12	5 Continues	Radiotherapy only locally helpful. Regression of nodes, skin plaques, oedema, and improvement in pleural effusion followed CB 1348. Fit to resume work
P. R.	F	44	6–10	0·15	350	5	Incapacitated. Not anaemic	2	5	4 Continues	Complete regression of spleen and nodes. Resumed household duties
I. W.	M	70	6–10	0·13	440	8	Seriously ill. Hb 50%	3	8	4 Continues	Resumed work 2 months after first dose. Regression of liver, spleen, nodes, oedema. Spleen enlarging 4 months.
S. V.	M	68	12	0·16	240	3	Seriously ill. Purpuric. Hb. 40%	1	2	0·5	Exacerbation of purpura precluded further treatment. Died 3 months later
H. W.	F	64	6	0·09	168	4	Good. Complained of enlarged nodes only	2	4	1	Improvement only slight and not maintained. Treatment discontinued on account of leucopenia. Subsequent temporary improvement after ^{32}P, which also induced leucopenia and purpura
P. P.	M	67	10	0·13	330	4	Fair. Neutrophil count 1,000 per c.mm. Hb. 66%	3	?	?	Neutropenia worse after CB 1348. Cellulitis from small septic focus responded to antibiotics. No follow-up
W. M.	F	67	4	0·1	190	7	Seriously ill. Hb 70%	Nil	Nil	Nil	No previous treatment. Disease present 3 years. Failed to respond to subsequent radiotherapy. Died 2 months after start of treatment
C. M.	F	70	10	0·14	212	4	Seriously ill. Hb 75%	,,	,,	,,	Responded 6 months previously to radiotherapy. Died 4 weeks after start of treatment

per c.mm. but the differential count remained abnormal throughout. His major disability has been associated with the chronic lung condition and he has required no further treatment for his leukaemia for four months after completing the first course.

2. Lymphocytic Lymphoma without Leukaemia

These 12 patients were closely similar to those with overt lymphocytic leukaemia. All had generalized lymph-node enlargement; some had enlargement of the liver and spleen; in all of five cases in which the bone marrow was examined heavy lymphocytic infiltration was present, but the peripheral leucocyte counts were normal or showed only moderate lymphocytosis. Seven patients had already had deep *x*-ray therapy. Before receiving treatment with CB 1348, 10 of the patients were incapacitated, six being seriously ill. Seven of these incapacitated patients, including three of those seriously ill, derived benefit from CB 1348. They have remained well and able to work for periods up to 27 months. Two of the remaining five patients responded for short periods only. The other three obtained no benefit. The results are summarized in Table III.

Thus 11 of the 20 patients with lymphocytic lymphoma, with and without leukaemia, obtained significant clinical benefit from CB 1348 treatment. In three cases radiotherapy had ceased to be effective, while in three treatment was successful in the presence of platelet counts between 45,000 and 100,000 per c.mm.

Follicular Lymphoma

All six patients had generalized lymph-node enlargement, five had splenomegaly and three had constitutional symptoms; three had at some stage moderate peripheral lymphocytosis, in one case up to 50,000 lymphocytes per c.mm. The daily dosage was 0.1–0.2 mg. per kg. Three patients were treated for four to seven weeks and three for 10 to 16 weeks. The total dosage was from 168 to 504 mg. Five patients derived benefit; symptoms were relieved and almost complete regression of spleen and nodes took place. Improvement started within three weeks of the beginning of treatment and progressed over the next few weeks. Four patients were moderately anaemic when treatment began, and in three of them the haemoglobin rose to the normal level. In the sixth case very small doses of CB 1348 were given because the patient was in a terminal neutropenic state and only short-lived benefit resulted.

One patient has remained free of recurrence for 20 months without further treatment. One has a few palpable lymph nodes after 16 months. In another, recurrences appeared after a year, but further treatment was postponed until symptoms returned two years after the initial treatment was completed. A good response was obtained to a second course of CB 1348 (0.05 to 0.1 mg. per kg. for 56 days) in this patient and in another who developed generalized recurrence 2¼ years after the first course (0.1 mg. per kg. for 28 days).

CB 1348 has been as effective in follicular lymphoma as any other treatment; it is more convenient than radiotherapy, less disturbing to the patient than mustine, and safer than T.E.M.

Reticulum-cell Sarcoma

These 11 patients had rapidly progressive disseminated disease that had begun as locally invasive focal lesions except in one case in which multiple metastases were present when medical advice was sought. In three cases the histological picture, though pleomorphic and essentially undifferentiated, showed some lymphoid maturation. Seven patients had previously been treated with radiotherapy or radioactive phosphorus.

Treatment with CB 1348 led to some improvement in six cases. In three the effects of treatment were striking, but improvement was not maintained longer than three months and there was no response to subsequent courses. In a cachectic patient with extensive skin involvement complete regression of lesions with healing of secondarily infected ulcers followed treatment with large intravenous doses of CB 1348, but agranulocytosis and thrombocytopenia ensued.

Exfoliative Erythrodermia

Remarkable but short-lived improvement took place in the patient with exfoliative erythrodermia, radioactive phosphorus having been ineffective. Similar transient improvement was later observed after treatment with radioactive arsenic.

Toxic Effects on Blood Elements

Lymphocytes.—Many patients showed lymphopenia during treatment, usually slowly progressive, though irregularly so and continuing as long as the drug was given. Sometimes lymphocytes disappeared from the blood. After treatment normal levels were usually rapidly regained.

Neutrophils.—Most patients showed some neutropenia after the third week of treatment. Falls of 20–60% from pretreatment neutrophil counts were common and recovery was rapid. In one case the neutrophil count continued to fall for 28 days after treatment was stopped, but in no other instances did neutropenia continue for more than 10 days after the last dose. Eleven patients developed more severe neutropenia, but two had 1,000 neutrophils per c.mm. or less before treatment. In the others the neutrophil count fell to 1,000 per c.mm. or less, representing a fall 85–95% below pretreatment levels. Five patients recovered rapidly; the others were all in the terminal stage of their disease and at the time of death were still neutropenic. This severe neutropenia was closely related to the dosage of CB 1348 (Table IV), for all but one patient received a total dose of

TABLE IV.—*Incidence of Severe Neutropenia* in 60 Patients† Treated with CB 1348. Relation to Dosage*

	No. of Patients	Total Dose of CB 1348			
		500 mg. or More	Less than 500 mg.	6·5 mg. per kg. Body Weight or More	Less than 6·5 mg. per kg. Body Weight
Developing severe neutropenia ..	9	6 (4)	3	8 (5)	1
Not developing severe neutropenia ..	51	18 (9)	33	22 (11)	29
Total	60	24 (13)	36	30 (16)	30

* Severe neutropenia is recorded when neutrophil count is 1,000 per c.mm. or less.

† Two patients with severe neutropenia before treatment are omitted.

Figures in parentheses represent numbers of patients who received total dose in 8 weeks or less.

6.5 mg. per kg. or more (450–550 mg.) in one course. The remaining patient received 5.7 mg. per kg. in eight weeks. About a quarter of all patients receiving 6.5 mg. per kg. may be expected to develop severe neutropenia, and if this dose is taken in eight weeks or less the proportion approaches one-third. It may be significant that 16 of the 20 patients who derived most benefit from treatment received comparatively small doses, and this suggests that administration of CB 1348 need not be pushed to its limits of tolerance to achieve the best therapeutic results.

Patients with carcinomatosis tolerate larger doses with less risk of haematological depression. One patient with advanced carcinoma of the rectum was given 2.23 g. (32 mg. per kg.) in eight months without any effect on the blood picture. However, a patient with extensive skeletal metastases from anaplastic carcinoma of the fundus uteri who received only 120 mg. of CB 1348 in three days (approximately 3 mg. per kg.) suffered a 75% depression of neutrophils, to fewer than 1,000 per c.mm. The platelet count fell to 60,000 per c.mm. In the lymphoma group most patients who developed severe neutropenia and thrombocytopenia had infiltration of the bone marrow, but others who tolerated the drug well had similar infiltration.

Platelets.—Platelet depression was rarely serious in patients treated with CB 1348. In 11 cases treatment was given although the platelet count was below 100,000 per c.mm. Five were cases of chronic lymphocytic leukaemia and in three treatment led to a sustained rise in the platelet count to above 100,000 per c.mm. (Cases 5, 6, and 7). In Case 7 this rise was preceded by a brief purpuric phase during which the platelet count was further depressed. These were three of the patients who responded best to CB 1348. The platelet count was unaffected in the fourth case and continued to fall in the fifth. In two of the remaining six patients given CB 1348 despite pre-existing thrombocytopenia there was further depression of the platelet count.

Discussion

The disadvantages of existing methods of treatment of the lymphomas are well known. A preparation of similar efficacy but lacking the side-effects and toxic properties of existing cytotoxic drugs would find a place in therapeutics. To some extent CB 1348 fulfils these requirements. It is relatively free from side-effects: from our limited experience it is at least as effective as any other method in follicular lymphoma and in lymphocytic lymphoma. In the latter group particularly, treatment by conventional agents is often unsuccessful because dosage is limited by thrombocytopenia, or in the subleukaemic group by low leucocyte counts; yet CB 1348 has been used successfully in these circumstances. In Hodgkin's disease the proportion of patients who responded well is small; but useful remissions have been obtained, in two instances better than those following T.E.M. CB 1348 is safer than T.E.M.: this is especially important when repeated courses are required, for it is rarely safe to give more than three courses of T.E.M. Unexpected and irreversible bone-marrow damage following previously well-tolerated doses of T.E.M. is not uncommon even when the blood picture is apparently normal before treatment (Haddow, 1953; Nabarro, 1953). With CB 1348 up to six courses have been given safely. Severe bone-marrow damage can follow CB 1348 administration, but it is usually the result either of excessive dosage or of treating patients with impaired bone-marrow function.

The dosage likely to cause bone-marrow damage almost always lies well outside the therapeutic range, at any rate for first courses. For these reasons we believe CB 1348 deserves further trial in the treatment of malignant lymphoma.

Suggestions for the Routine Use of CB 1348

CB 1348 may be safely used in routine therapy if simple precautions are taken to avoid damaging the bone marrow. The marrow is especially vulnerable (1) shortly after a course of treatment with ionizing radiations or cytotoxic drugs, including CB 1348 itself; (2) when it is infiltrated with lymphomatous tissue; and (3) when it is hypoplastic as a result of long-standing and usually extensively treated disease. CB 1348 should therefore not be used within four weeks of the end of a full course of radiation therapy or chemotherapy.

When small doses of palliative *x*-radiation have been given over small fields remote from foci of bone marrow, the neutrophil and platelet counts will not usually be depressed and chemotherapy may be safely started. If one or both of these counts are depressed, treatment should be postponed until normal counts are obtained, usually one or two weeks later. Whether treatment has been given or not, persistently low neutrophil and platelet counts or peripheral lymphocytosis should lead to suspicion of bone-marrow infiltration. Marrow puncture should be performed in these cases. If lymphocytic infiltration is present, as is frequently the case in lymphocytic lymphoma and sometimes in follicular lymphoma, CB 1348 may be given, but at less than standard dosage. In some cases of Hodgkin's disease when marrow cannot be obtained from several sites by aspiration, trephine specimens may show extensive fibrosis. These cases are not suitable for chemotherapy.

The standard daily dose is 0.2 mg. per kg.; the whole dose is given at once and no special precautions are necessary. When lymphocytic infiltration of the bone marrow is present, or when the marrow is hypoplastic, the daily dose should not exceed 0.1 mg. per kg. Out-patient supervision is satisfactory in the less seriously ill patients, but during treatment approximately weekly visits are essential so that haemoglobin estimation and total and differential leucocyte counts can be performed; routine platelet counts may be omitted provided skin and mucous membranes are inspected for haemorrhagic phenomena. It is not safe to leave a patient for more than two weeks without clinical and haematological examination, and it is helpful to plot the blood counts at each attendance on a chart on which temperature, weight, and spleen size may also be recorded.

Clinical improvement is usually evident in the third week of treatment, but a four-weeks trial is necessary before giving up treatment as ineffective. Administration need not be discontinued as soon as the neutrophil count begins to fall, but it should be remembered that the fall may continue for 10 days after the last dose, and that as the total dose approaches 6.5 mg. per kg. there is a real risk of causing irreversible bone-marrow damage. An average course at 0.2 mg. per kg. per day might last four weeks (5.6 mg. per kg.). If maintenance therapy is contemplated in patients who show slowly progressive improvement during the initial weeks of treatment, who tolerate the drug well, and whose blood picture remains stable, the maintenance dose should not exceed 0.1 mg. per kg. per day, and may well be kept at 0.03 mg. per kg. It is probable that short courses of treatment carry less risk than maintenance therapy. Both methods have been effective; but it is possible that continuous therapy may give an illusion of "maintenance" to a remission that would have proceeded without further treatment.

Summary

Sixty-two patients suffering from malignant lymphoma have been treated with *p*-(di-2-chloroethylamino)-phenylbutyric acid (CB 1348), a water-soluble aromatic nitrogen mustard. There were 23 patients with Hodgkin's disease, 11 with reticulum-cell sarcoma, 12 with lymphocytic lymphoma, 8 with chronic lymphocytic leukaemia, 6 with follicular lymphoma, 1 with mycosis fungoides, and 1 with exfoliative erythrodermia.

Striking remissions were obtained in four cases of Hodgkin's disease, seven of lymphocytic lymphoma, four of chronic lymphocytic leukaemia, and five of follicular lymphoma.

CB 1348 therapy is relatively free from gastro-intestinal side-effects and has proved to be less damaging to haemopoietic tissue than cytotoxic agents hitherto available for the treatment of malignant lymphoma.

This investigation has been supported by grants to the Chester Beatty Research Institute from the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund for Medical Research, the Anna Fuller Fund, the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service, the Manitoba Cancer Institute, and the Clinical Research Committee of the Middlesex Hospital. We thank Dr. P. E. T. Hancock and Dr. J. B. Harman for much advice; the consultant staff of the Royal Marsden Hospital for allowing us to treat their patients; Dr. Gwen Hilton, Dr. A. L. Jacobs, Dr. J. L. Livingstone, Mr. S. Farrant Russell, Dr. J. G. Scadding, and Dr. B. Buckley Sharp for referring patients. We also thank the Wellcome Foundation for supplying CB 1348, Mr. J. H. Wood and his staff for making the tablets, and Dr. I. Lewin for reading the typescript.

References

Everett, J. L., Roberts, J. R., and Ross, W. C. J. (1953). *J. chem. Soc.*, p. 2386.
Haddow, A. (1952). *A.R. Brit. Emp. Cancer Campgn.* **30**, 25.
—— (1953). *Proc. roy. Soc. Med.*, **46**, 692.
Nabarro, J. D. N. (1953). Ibid., **46**, 696.

RECENT STUDIES ON ALBOMYCIN, A NEW ANTIBIOTIC

BY

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Albomycin, a new antibiotic, has been manufactured during recent years by the pharmaceutical industry of the Soviet Union. It has been studied both in the laboratory and in clinical practice, and it is the purpose of this paper to summarize the results of the most important studies.

Origin and Chemical Nature

Albomycin was obtained by Gause and Brazhnikova (1951) from cultures of a new species of streptomycetes, *Actinomyces subtropicus*. This antibiotic strongly inhibits the growth of Gram-positive cocci, chiefly pneumococcus and staphylococcus. More important, it inhibits the growth of staphylococci resistant to other antibiotics, including penicillin, streptomycin, the tetracyclines, and erythromycin. It is also effective against a number of Gram-negative bacteria—for instance, the coli-dysentery group of organisms and Friedländer's bacillus. Pure albomycin inhibits the growth of staphylococci in a dilution of 1 in 700 millions, whereas crystalline penicillin inhibits their growth in a dilution of 1 in 80 millions. In other words, 1 mg. of albomycin inhibits the growth of staphylococci about ten times more strongly than an equal amount of penicillin. Albomycin was found to be practically non-toxic for animals and in clinical practice, and it was therefore studied in greater detail.

Data on the chemical nature of albomycin were published by Brazhnikova, Lomakina, and Muravieva (1954). The isolation of chemically pure albomycin from the culture fluid of *Actinomyces subtropicus* presents difficulties which can be overcome in a number of ways. Albomycin is a basic substance and forms salts with various acids. Chemically pure sulphate of albomycin is in the form of an amorphous red powder, easily soluble in water, slightly soluble in methanol, but insoluble in other organic solvents.

The pure preparation of albomycin sulphate contains 4.16% of iron. Experiments have shown that it is possible to remove iron from the molecule of albomycin by treating it with acetone containing hydrochloric, hydrobromic, or hydriodic acid or with oxychinolin. Under this treatment the bright orange colour of albomycin solutions disappears and their antibacterial activity is reduced 14 to 15 times. When, however, a drop of 5% solution of ferric chloride is added to the watery solution of the inactivated albomycin, both colour and antibacterial activity are completely restored. Hence the iron content of albomycin represents a labile functional group, which can be split off in acetone media in the presence of hydrohalogen acids. When albomycin solution in acetone is acidified with sulphuric or nitric acid, or if ethanol is used instead of acetone, the splitting of iron is not observed. It seems probable that the iron is attached by a chelate bound to the hydroxy group of serine, which is contained in the molecule of albomycin.

Pure albomycin gives a positive biuret reaction; it contains 13.28% of total nitrogen (Kjeldahl) and 1.34% of amino-nitrogen (Van Slyke). During the first five minutes 1.22% of amino-nitrogen can be determined, and during the next 25 minutes only 0.12%. When albomycin is subjected to hydrolysis by hydrochloric acid for 26 hours the amount of amino-nitrogen increases from 1.34% to 7.2%. Hydrolysate of pure albomycin contains a number of amino-acids; therefore this antibiotic may be said to belong to the class of metal-containing peptides.

From the fact that pure albomycin gives a negative reaction with ninhydrin, and that this becomes positive only after slight heating with dilute hydrochloric acid, it can be concluded that albomycin does not contain free α-amino groups, the latter appearing only after hydrolysis. Albomycin appears to be a cyclopeptide. It has been shown that it contains a free amino group which participates in the formation of salts. When albomycin is deaminated under mild conditions its antibacterial activity is completely lost.

If the equivalent weight of albomycin is calculated on the assumption that the molecule of this antibiotic contains one atom of iron, one residue of sulphuric acid, and one amino group, the values 1346, 1336, and 1270 are obtained. This indicates that the molecular weight of albomycin is not less than 1300.

TABLE I.—*Amino-acid Composition of Albomycin*

Rf	Butanol–Water–Acetic Acid		Water-saturated Phenol–Ammonia	
	Pure Amino-acid	Albomycin Hydrolysate	Pure Amino-acid	Albomycin Hydrolysate
Ornithine	0·12	0·12	—	—
Serine	0·20	0·194	0·34	0·34
Glutamic acid	0·23	0·24	—	—
Alanine	0·273	0·288	0·57	0·57
Proline	0·35	0·36	0·81	0·81
Glycine	0·25	0·26	0·35	0·37

TABLE II.—*Amino-acid Composition of Albomycin (Two-dimensional Chromatograms)*

Rf Butanol / Rf Phenol	Albomycin Hydrolysate	Pure Amino-acid
Ornithine	0·21	0·18
Serine	0·62	0·61
Glutamic acid	0·20	1·20
Alanine	0·60	0·59
Proline	0·45	0·45
Glycine	0·70	0·71

Chromatographic studies (Tables I and II; Fig. 1) have shown that the hydrolysates of albomycin contain seven amino-acids. Six of these have been identified with ornithine, serine, glutamic acid, alanine, glycine, and proline; the seventh has not so far been identified with any of the known amino-acids. The amount of serine and ornithine in the molecule of albomycin is greater than that of the other amino-acids.

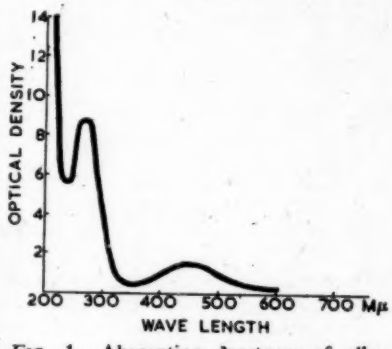

FIG. 1.—Absorption spectrum of albomycin.

It can therefore be concluded that albomycin differs significantly in chemical structure from the other antibiotics so far described; it also differs markedly from griseine, the only iron-containing antibiotic produced by an actinomycete.

Mechanism of Antibacterial Action

Study of the sensitivity to albomycin of the commoner bacteria has shown that the following are sensitive: staphylococci, *Escherichia coli, Aerobacter aerogenes, Sarcina subflava,* and *Bacillus subtilis* (Gause and Brazhnikova, 1951). Further, pneumococci, *Klebsiella,* dysentery bacilli, and some (but not all) strains of *Streptococcus pyogenes* are very sensitive. Somewhat less sensitive are meningococci and *Haemophilus pertussis* (Shorin, 1951). Albomycin strongly inhibits *Spirochaeta sogdianum in vivo.* The following are insensitive to albomycin: *Listerella,* tubercle bacilli, and *Bacillus mycoides.*

An analysis was also made of the incidence of albomycin-resistant strains of staphylococci in various infections in

clinical practice. It was found that about 31% of strains are resistant to penicillin, and about 1% resistant to albomycin. Strains resistant to albomycin were found to be penicillin-sensitive (Shorin, 1951).

The mechanism of the antibacterial action of albomycin is interesting. Its action on the respiration of staphylococci and *E. coli* has been shown to be a typically bacteriostatic one (Sazykin, 1955). It was observed by Shorin and Sazykin (1954) that albomycin, independently of concentration, inhibits the growth of staphylococci, *E. coli*, and other bacteria only in the presence of oxygen. In these experiments narrow glass tubes containing agar nutritive medium were before inoculation placed for 20–30 minutes in a boiling water-bath to eliminate air from the agar, and afterwards rapidly cooled to 45°–50° C. At this temperature two or three drops of bacterial suspension were put into each test-tube together with the necessary amount of albomycin dissolved in 0.1 ml. of sterile distilled water. The medium in the test-tubes was then carefully mixed by shaking, precautions being taken to avoid air bubbles forming in the agar. Afterwards the tubes were cooled until the agar solidified and then incubated at 37° C. for 24 hours.

It was observed that albomycin inhibits the growth of bacteria only in the upper layer of the agar medium—that is, under aerobic conditions. In the bottom layer of the agar in the narrow test-tubes, where the oxygen does not penetrate, the growth of bacteria is not inhibited by any concentration of albomycin up to 5,000 units per ml., the greatest concentration tested (Fig. 2).

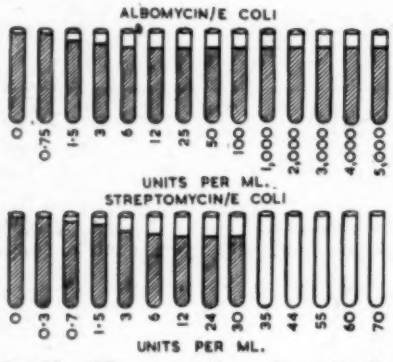

FIG. 2.—Effect of albomycin and of streptomycin on growth of *E. coli* in nutritive agar.

That albomycin inhibits the growth of sensitive bacteria only in the presence of oxygen leads to the conclusion that it is active only when the bacterium is breathing with the aid of the oxygen-transporting enzyme, which, as is well known, contains iron in its molecule. The hypothesis may be advanced that the structure of albomycin is similar to that of some component of the iron-containing respiratory system of the bacterial cell, and hence that it impedes the working of this system and interferes with the growth of the bacteria. In the absence of oxygen the respiration of the sensitive bacteria takes some other course; the iron-containing oxygen-transporting enzyme is no longer involved in the process of respiration, and it is no longer possible for the albomycin to exert its antibacterial action.

It is to be expected that increasing the concentration of iron in the nutritive medium of staphylococci growing in Petri dishes will increase the concentration of the respiratory enzyme in their cells, and in this way decrease the action of albomycin on staphylococci as measured by the agar diffusion method. It was actually observed by Brazhnikova that by adding 0.04% of ferric chloride to the nutritive-agar medium upon which staphylococci are growing the action of albomycin upon these organisms is decreased by about 30%.

On the basis of the above data the molecule of albomycin may be considered as an "imitation" of some iron-containing respiratory enzyme of the sensitive bacteria, in which iron functions as a prosthetic group and the polypeptide part as a protein carrier. This being so, further investigation of the structure of albomycin and of the type of binding of iron with the polypeptide rest of the molecule could be of immediate theoretical interest for the study of the respiratory enzymes and for the understanding of the process of respiration in bacteria.

Pharmacological Properties

The absence of toxicity of albomycin has been demonstrated both experimentally in animals and clinically. It is impossible to determine the lethal dose of the antibiotic for mice, rabbits, cats, or guinea-pigs. It is well tolerated when injected subcutaneously or intravenously in the maximum concentrations tested—that is, 50 million units per kg. of body weight (mice). As regards absence of toxicity albomycin can be compared only with penicillin. It is interesting to note that the drug is also well tolerated by guinea-pigs, for which penicillin is rather toxic.

Albomycin is pharmacologically inactive (Shorin, 1951); intravenous injections of large doses in animals do not affect the heart, blood pressure, or respiration. It is devoid of cumulative toxicity and pyrogenic action, and no local reactions are observed when it is injected subcutaneously or intramuscularly in animals or man. The intrathecal injection of albomycin is safe and not accompanied by any side-reaction. Histological examination of organs and tissues of laboratory animals given daily injections of large doses of albomycin for a considerable period (up to 30 days) did not reveal any deviations from the normal. The composition of blood and the activity of leucocytes are also not affected by albomycin (Rossolimo, 1951). Complete absence of toxicity of the drug for man is also proved by extensive clinical practice over several years.

A remarkable feature is the formation of a reversible complex between albomycin and serum proteins, which is of importance for its circulation in the body (Gause and Brazhnikova, 1951; Judinzev, 1951). Experiments have shown that its antibacterial action is not decreased when albomycin is used in 1% solution of casein or 10% solution of egg albumen. However, in the presence of 10% of blood serum, and particularly in whole serum, the antibacterial action of albomycin is reduced. This effect results from the partial and reversible binding of albomycin with the serum proteins. It is impossible to detect the presence of albomycin by the usual method of titration of this antibiotic with sensitive bacteria if its concentration in the serum attains 150 units per ml. or less. A greater concentration can be detected by the method of biological titration. Albomycin freely passes through collodion membranes, and experiments on its dialysis from solution in serum across such membranes have shown that the amount of antibiotic bound with proteins, and therefore non-dialysable, attains 100–200 units per ml. of horse serum, regardless of the amount of albomycin added to the serum.

The presence of active albomycin in the blood serum can be demonstrated in the following way. It has already been mentioned that if the concentration of albomycin attains 100 units per ml. of serum the latter is completely "inactive" so far as its antibacterial action is concerned. When, however, serum proteins containing "inactive" albomycin are sedimented by trichloracetic acid, the sediment removed by filtration, and the supernatant liquid neutralized, this liquid will retain in active form most of the albomycin which was initially added. In this way the antibacterial action of albomycin, at first "masked" by the serum, can be completely restored after sedimentation of the serum proteins (Gause and Brazhnikova, 1951). The method of estimating the concentration of albomycin in the blood serum is based on this principle. It is interesting that the complex of albomycin with serum proteins, if injected intraperitoneally into mice infected with pneumococci or dysentery bacilli, possesses chemotherapeutic activity. This experiment shows that the complex under investigation, inactive against bacteria *in vitro*, is capable of dissociation *in vivo* with reappearance of the antibiotic in the active form (Shorin, 1951).

The experiments above outlined are important for explaining the specific features of the circulation of albomycin in the body. It was observed by Judinzev (1951) in experiments with rabbits that after the first subcutaneous injection the amount of albomycin excreted by the kidney was not

great, because it is partially bound with proteins. After repeated injection the amount of albomycin excreted by the kidney increases sharply, since the serum proteins are already saturated with the antibiotic and the latter appears in the form of a "free" compound. One unit of albomycin inhibits the growth of staphylococci in 1 ml. of nutritive agar, and is approximately equal to 1/50 unit of penicillin. After subcutaneous injection into a rabbit of 100,000 units per kg. body weight albomycin circulates in the blood for three days. The maximum concentration of albomycin in the blood (240 units per ml.) is attained within 30 minutes of subcutaneous injection. Thereafter the concentration gradually decreases, and at the end of the fourth hour reaches 150 units per ml., and at 24 hours 100 units per ml. (Fig. 3). Albomycin remaining free and not bound by serum proteins is usually excreted in the urine for six to eight hours after injection (usually 70 to 80% of the injected dose), while the protein-bound albomycin is slowly excreted from the organism for two or three days. Albomycin can be detected in the lymph, and penetrates well into various organs and tissues; it is, however, unable to pass into the cerebrospinal fluid (Judinzev, 1954).

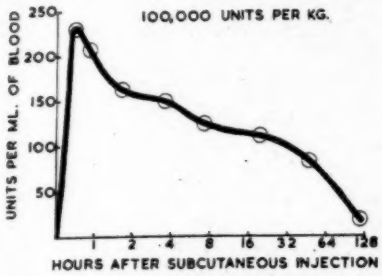

FIG. 3.—Concentration of albomycin in blood of rabbit after single subcutaneous injection of albomycin in a concentration of 100,000 units per kg.

Chemotherapeutic Investigations

It has been shown by Shorin (1951) in experiments in mice infected with 500,000 lethal doses of pneumococci that 100% survival can be obtained with a single subcutaneous injection of 750,000 units of albomycin per kg.; in parallel experiments with penicillin only 20% survival was observed. In experiments in mice infected with various strains of staphylococci and haemolytic streptococci injection of albomycin invariably yielded positive therapeutic results. In mice infected with virulent strains of dysentery bacilli a single injection of albomycin had the same effect as injection of an equal amount of streptomycin. In guinea-pigs infected with *Sp. sogdianum* both the blood and the brain became sterile after treatment with albomycin in a dosage of 150,000 units per kg. daily for 14 days. When equal amounts of penicillin were used (in dilution units = 1/50 of Oxford units) the results were manifestly inferior. In mice infected with 50 lethal doses of Friedländer's bacillus a single subcutaneous injection of 25,000 units of albomycin per kg. led to 100% survival; when the number of lethal doses was increased to 500 the amount of albomycin required to attain the same effect was increased four times —that is, to 100,000 units per kg.

In experimental infection of animals with tubercle bacilli, *Listerella, Salmonella,* and *Rickettsia,* albomycin was found to be ineffective.

The action of albomycin combined with other antibiotics was studied in experiments in mice infected with pneumococci, it being relatively easy in these circumstances to vary the number of lethal doses and to attain quantitative results. It was recorded that the action of albomycin *in vivo* in combination with penicillin or with streptomycin is clearly synergistic.

Clinical Application

In clinical practice albomycin is used mainly in the treatment of various infections caused by pathogenic cocci. In paediatrics it is used in the treatment of pneumonia, particularly in young children. Positive therapeutic results were obtained in the septic complications of dysentery and measles and in various septic conditions caused by penicillin-resistant bacteria (Sokolova and Smirnova, 1953; Dobrochotova, 1951; Krechmer *et al.*, 1951; Raicher, 1952; and Shapiro, 1951). Intrathecal injections of albomycin have given good results in the treatment of meningitis caused by penicillin-resistant pneumococci. No side-reactions were recorded after intrathecal injections of 100,000–200,000 units of albomycin in children. Gilevich (1953) has shown albomycin to be very effective in the treatment of relapsing fever due to *Sp. sogdianum,* the dosage for adults being 3 million units intramuscularly twice a day for 7–12 days.

Zemskov (1953) and Selzovsly have demonstrated the activity of albomycin in the treatment of peritonitis and other surgical infections. Berent and Gilman (1954) used albomycin to treat prostatitis and gonococcal urethritis caused by penicillin-resistant bacteria. As is evident from the number of papers published, the use of albomycin in clinical practice is gradually extending.

Summary

Results of laboratory and clinical investigations of albomycin, a new antibiotic prepared in the U.S.S.R. from *Actinomyces subtropicus,* are presented.

Albomycin is effective against a variety of organisms, and particularly against staphylococci resistant to other antibiotics. Its action is about ten times as strong as that of penicillin.

Its chemical nature and pharmacology are discussed.

It forms a reversible complex with the serum proteins, which facilitates its circulation in the body. It is non-toxic, and well tolerated in large doses—up to 50 million units per kg.—given subcutaneously or intravenously. No side-reactions were noted after intrathecal injections in children.

Albomycin has proved effective in the treatment of pneumonia, especially in young children, in the septic complications of dysentery and measles, and in meningitis due to penicillin-resistant pneumococci. It has also been used in the treatment of peritonitis and other surgical infections, and for penicillin-resistant prostatitis and gonococcal urethritis.

References

Berent, I. E., and Gilman, K. S. (1954). *Sovetsk. Med.*, No. 7, 34.
Brazhnikova, M. G., Lomakina, N. N., and Muravieva, L. I. (1954). *Compt. rend. Acad. Sci. U.R.S.S.*, **99**, 827.
Dobrochotova, A. I. (1951). *Nov. Med. (Mosk.)*, **23**, 35.
Gause, G. F., and Brazhnikova, M. G. (1951). Ibid., **23**, 3.
Gilevich, Y. S. (1953). *Med. Parazit.*, **5**, 433.
Judinzev, S. D. (1951). *Nov. Med. (Mosk.)*, **23**, 22.
—— (1954). *Compt. rend. Acad. Sci. U.R.S.S.*, **99**, 115.
Krechmer, B. B., *et al.* (1951). *Sovetsk. Med.*, No. 10, 10.
Raicher, E. A. (1952). Ibid., No. 11, 18.
Rossolimo, O. K. (1951). *Nov. Med. (Mosk.)*, **23**, 30.
Sazykin, Y. O. (1955). *Mikrobiologija*, **24**, 75.
Shapiro, S. L. (1951). *Nov. Med. (Mosk.)*, **23**, 53.
Shorin, V. A. (1951). Ibid., **23**, 7.
—— and Sazykin, Y. O. (1954). *Compt. rend. Acad. Sci. U.R.S.S.*, **96**, 645.
Sokolova, K. F., and Smirnova, M. K. (1953). *Pediatrija*, No. 1, 23.
Zemskov, N. N. (1953). *Vrac. Delo*, **5**, 425.

To allow blind physiotherapists to give ultraviolet light therapy with the same accuracy and confidence as their sighted colleagues an electrical apparatus has been evolved, the "erythema meter," which measures the degree of redness of the patient's skin. Essentially it consists of a photoelectric detector which converts colour impressions to sound signals; thus a blind operator can tell, by comparing control non-irradiated skin with the irradiated area, whether his patient is in danger of receiving too heavy a dose. The "erythema meter," which is quite small and compact, was designed and made by Electro-Medical Supplies (Greenham), Ltd., in conjunction with the Royal National Institute for the Blind, the Institute also providing a research grant for the work. The apparatus has been approved by a panel of the Chartered Society of Physiotherapy, and steps are now being taken to train blind physiotherapists in its use.

CONJUNCTIVAL BIOPSY IN SARCOIDOSIS

BY

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This is a preliminary report of a rapid and easy method of confirming the diagnosis in patients with suspected sarcoidosis. Isolated cases of conjunctival sarcoidosis have been described from time to time, but the condition has generally been believed to be quite rare (Woods, 1951). On the contrary, we have so often found it in patients with generalized sarcoidosis that conjunctival biopsy would appear to have diagnostic value even when

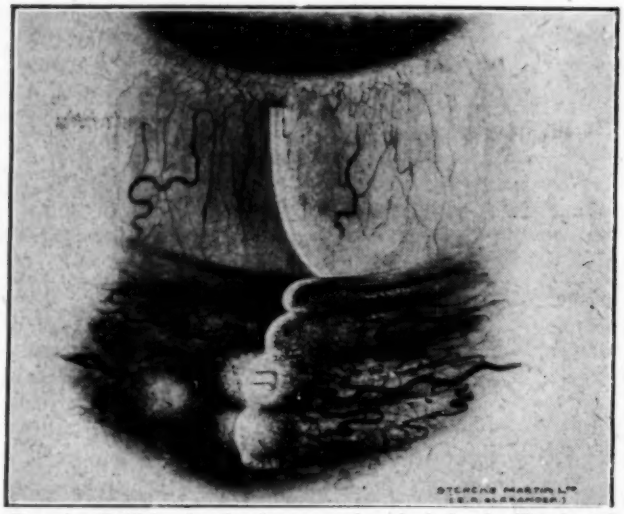

FIG. 1.—Follicles in the lower conjunctival fornix illuminated by the slit-lamp beam, the lower lid being everted. (Approximately ×12.)

there are no ocular symptoms. The method was developed after seeing a patient who presented with follicles in the fornix and bulbar conjunctiva and who was found to have generalized sarcoidosis (Crick and Mather, 1954). A conjunctival biopsy revealed epithelioid cell structures typical of sarcoidosis, which were also found in the liver and lymph nodes. These sarcoid lesions show no caseation, are composed predominantly of reticulo-endothelial ("epithelioid") cells with occasional multinucleate giant cells, and are surrounded by a narrow zone of lymphocytes and fibroblasts. Subsequently, isolated follicles were seen during routine slit-lamp examinations of patients with sarcoidosis (Fig. 1). Biopsy of these demonstrated sarcoid lesions similar to those already seen in other tissues. The method was then used in an attempt to separate uveitis caused by sarcoidosis from other forms. Finally, conjunctival biopsies were used as a means of histological confirmation of sarcoidosis in patients thought to have the disease, even though there was no obvious ocular involvement, but in whom biopsies elsewhere were either not possible or else had proved negative.

The follicles are just visible to the naked eye, but are best seen with the slit-lamp: sometimes they are confluent. They are small elevations which are translucent and slightly yellow in colour. Follicles are usually found in the fornices, but may be encountered in the bulbar conjunctiva, sometimes as part of a sclerokeratitis (Fig. 2). Examples of such lesions in the bulbar conjunctiva have recently been reported (Ashton, 1954; Klein *et al.*, 1955; Crick, 1955). When examined microscopically the follicles may be seen to contain sarcoid lesions resembling those in other organs, but

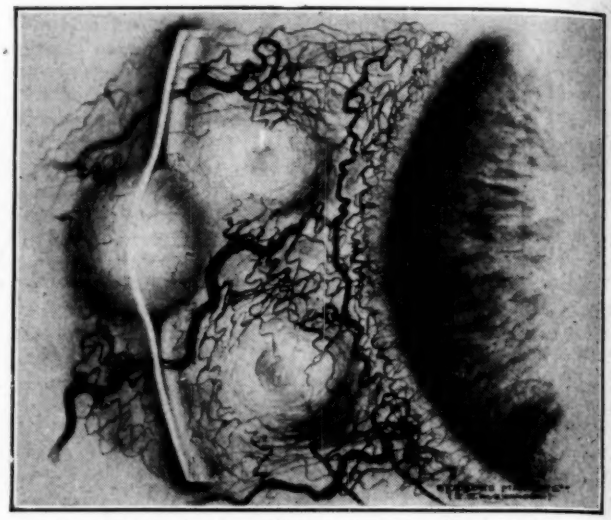

FIG. 2.—Follicles in the bulbar conjunctiva illuminated by the slit-lamp beam. (Approximately ×12.)

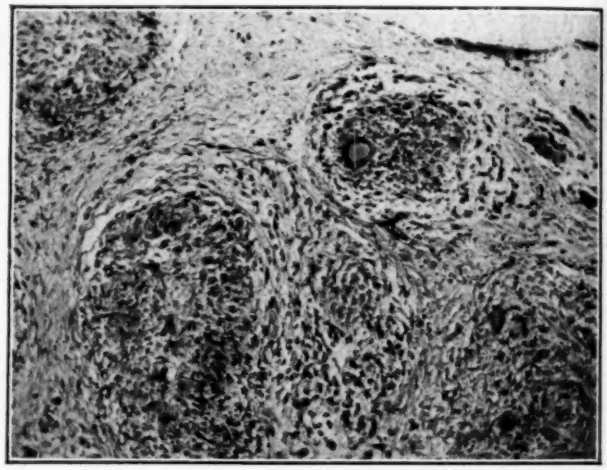

FIG. 3.—Conjunctival biopsy showing several epithelioid cell granulomas. (H. and E. stain. ×75.)

are often surrounded by the lymphocytes that are so common in the subconjunctival connective tissue (Fig. 3). Biopsy material occasionally contains lymphoid tissue with germinal centres which should not be confused with sarcoid lesions.

Methods and Results

Three drops of 4% cocaine solution are instilled into the conjunctival sac at two-minute intervals. A small fold of fornix conjunctiva about 2 mm. long containing follicles is grasped with forceps and snipped off with one cut of the scissors. There is usually no pain, but occasionally a momentary prick is felt. A suture is unnecessary and there is little haemorrhage—at the most slight capillary oozing. Chloramphenicol ointment 1% is applied but no dressing is required. The site of the biopsy heals completely in a few days and neither infection nor symblepharon has occurred.

The specimen is fixed in formol-saline and 50 serial sections are cut and examined from each.

The procedure for biopsy of the bulbar conjunctiva is similar except that a conjunctival suture is required to prevent retraction of the edges of the incision and the eye is kept covered for two or three days.

Twenty-eight conjunctival biopsies have been done. Ten were on material from patients with generalized sarcoidosis without ocular symptoms. Sarcoid lesions were found in three: one of these had histological confirmation by a liver biopsy and another showed typical sarcoid lesions in the conjunctiva even though a previous liver biopsy had not done so. Eighteen were patients who presented with uveitis or episcleritis of a type which suggested the possibility of sarcoidosis. Six of these were found to have generalized sarcoidosis, and four of the six had a positive conjunctival biopsy. The remaining 12 had no signs of systemic sarcoidosis, but in three of these typical sarcoid lesions were found at the biopsy. Thus in 16 patients with the generalized disease a positive conjunctival biopsy was obtained in seven.

Comment

Interpretation of the histology is more difficult than in liver or lymph nodes owing to the normal presence beneath the conjunctival mucous membrane of chronic inflammatory cells and lymphoid tissue. It is for this reason that serial sections are essential, also familiarity with the histology of sarcoidosis elsewhere. Sometimes a suspicious collection of cells proves to be the edge of a sarcoid lesion when it is traced through serial sections; on other occasions the appearance remains non-specific.

Conjunctival biopsy is a simple procedure which can be done in the out-patient department, and hence has an advantage over liver and lymph-node biopsy.

Our results also show that typical sarcoid lesions occur in a significant proportion of patients. For these reasons conjunctival biopsy warrants further trial as a means of obtaining histological evidence of sarcoidosis.

Summary

Conjunctival lesions in sarcoidosis are more common than has hitherto been suspected. A simple method of conjunctival biopsy is described which has been used in 28 cases suspected of having the disease. Results so far suggest that the procedure will prove to be of diagnostic value in sarcoidosis.

We wish to thank Professor H. A. Magnus and the medical and technical staff of his department for the histological preparations and their interpretation, and Mr. E. R. Alexander and Mr. W. Smith for the illustrations.

References

Ashton, N., Acta XVII int. Congr. Ophthal. (Montreal-New York, 1954). In press.
Crick, R. P. (1955). *Trans. ophthal. Soc. U.K.* In press.
—— and Mather, H. G. (1954). *Brit. J. Tuberc.*, **48**, 204.
Klein, M., Calvert, R. J., Joseph, W. E., and Smith, E. (1955). *Brit. J. Ophthal.*, **39**, 416.
Woods, A. C. (1951). *"Sarcoidosis" in Systemic Ophthalmology*, edited by A. Sorsby, p. 195. Butterworth, London.

The London County Council's "Safety in the Home" week, starting on November 14, is intended to arouse public awareness to the dangers of accidents in the home, and to suggest ways and means of reducing the alarming number of deaths and injuries. Special emphasis will be laid on the avoidance by simple precautions of hazards which result in burns and scalds. There will be a "Burns and Scalds" exhibition during the week, in the Belvedere Road entrance to the County Hall. As well as the widespread use of posters and leaflets, a short film called "Dangerous Ages" will be shown at a number of London cinemas.

SOME PROBLEMS IN THE MANAGEMENT OF THE AGED*

BY

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When it was suggested that I should contribute a paper at the Joint Meeting, the choice of a subject gave me much thought, for I have no academic background, and have, for 35 years, been engaged only in general practice, a sphere in which the art of medicine is perhaps as important as the science. In recent years the study of geriatrics has assumed an ever-increasing importance in our everyday life and has brought home to all of us the inevitability of old age; so it may be of interest to those living in a more free political economy to hear of some of the difficulties which old age presents in the Welfare State. Socialized or nationalized medicine is now a feature of political propaganda in almost every educated country, and in the foreseeable future you, in Canada, are almost bound to be faced with some form of national health and welfare services, and, if so, you may benefit greatly from our mistakes. I do not pretend to tell you anything you do not already know. I shall only try to indicate some of the difficulties we in Britain are endeavouring to solve.

"Grow old along with me. The best is yet to be. The last of life for which the first was made." So wrote Robert Browning. But if we are to travel to these Elysian Fields we must make adequate preparations for the journey. As a family doctor, I have been consulted on many occasions by those approaching retirement on how they can attain that "unhoped serene that men call age" with a peaceful, happy, and contented mind. I tell them: (1) have at least one ambitious project you would like to attain; (2) consider your income and draw up a tentative budget of expenditure—financial worries are a very big source of misery and unhappiness, leading to mental and physical ill-health; (3) envisage how you will spend your enforced leisure and draw up a tentative programme for your activities, but please make it flexible and elastic—the most unhappy old people I know are those who strive to live by rule and rote; (4) make a point of helping others and undertake some form of social work to avoid the awful evil of self-absorption, remembering that "age is opportunity no less than youth itself though in another dress, and as the evening twilight fades away the sky is filled with stars invisible by day." What, then, do we mean by old age? There is still much truth in the Biblical definition, "The days of our years are threescore years and ten; and if by reason of strength they be fourscore years, yet is their strength labour and sorrow."

A Mounting Problem

In Britain, administratively, we regard women at 60 and men at 65 as having reached an age justifying retirement and qualifying to draw an old age pension. Our most recent census, in 1951, showed that 12% of the population came into this category, but, of these, over 1,000,000 remained at work. The expectation of life has increased considerably in the past two decades and far exceeds the old Hindu adage which divided the span of life into "Twenty years to learn, twenty years to work, and twenty years to pray." In 1941 there were in Britain four and a half million people over

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65, and it is estimated that by 1971 there will be nine and a half million. Unless, then, the retiring age is raised, obviously the magnitude of the problem will constitute a very severe drain on the country's economy and prove an almost intolerable burden for the working population.

For some reason that no one has yet elucidated, women live appreciably longer than men. In 1954 the average expectation of life was 68 for men and 71 for women, as compared with 1931, when it was 59 for men and 63 for women. The dangers associated with child-bearing have been greatly reduced, and in the past decade the number of women who continue at work after marriage, and indeed are undertaking two full-time jobs, has steadily increased. Some research into the working hours of men and women respectively, into the responsibilities assumed by each sex, into the incidence of illness and the length of incapacity, might yield some startling information and force us to the conclusion that men were, in fact, the weaker sex.

Cause of Senescence

It is perhaps reasonable to say that we begin to age about 60, even although we are not likely to become in any way dependent upon others until 70+. We all know innumerable sprightly septuagenarians and many active octogenarians, but ageing must be admitted when our physical powers decrease in vigour and our mental alertness begins to fail. What, then, is the cause of senescence? It is not a disease but rather a normal physiological stage of life just as natural as is growth and development in childhood. The essential change is a wastage of tissue which is either not repaired at all or is replaced by another and less useful tissue—muscle fibres being replaced by fat or fibrous tissue. The brain diminishes somewhat in size and contains less fat and more fluid—the gibe "water in the brain" has some physiological basis. Nerve cells and neurones atrophy; the myocardium undergoes fatty and fibrotic degeneration. Bones become more fragile. Cartilages become ossified. Synovial fluids dry up. The skin loses its softness. The ductless glands atrophy and their secretion lessens. The reproductive glands decline, and we now know that rejuvenation by hormones or transplants is an exploded hope. The arteries harden and the veins lose their tone. The harmonious co-operation of functions begins to fail; and the inherent store of energy becomes depleted and eventually falls below the level necessary to sustain life. Such is the physiological explanation of senescence—a slow but progressive wearing down until "death stands beside me whispering low, I know not what into my ear; of his strange language all I know is there is not one word of fear."

It is thus obvious that senescence is a very gradual thing and that many people can continue to work, though at a slower tempo, long after they are 65. How, then, are we to maintain and encourage them to remain employed? No one would suggest that a man who has worked his stint should be deprived of the right to retire while he still has vigour of mind and body to enjoy his leisure, but we can ask him if he really wants to retire. An interesting answer to that question was offered in Rutherglen, where a health centre for old age pensioners has been functioning for the past two years. Of 275 old people invited to express an opinion whether compulsory retirement was good or bad, 87% thought it was bad, 7% thought it was good, and 6% had no view to express.

Work for the Elderly

Pensionable age was fixed at a time when there was considerable unemployment and no antibiotics, but to-day there is full employment and the range of life-prolonging drugs is vastly extended. Every year medical science and improved housing and hygiene add a few months to the average citizen's expectation of life, and if this additional wealth of years is to be something other than labour and sorrow, then we must plan our economy so that the older members can still play an active part in the work and production of the country. For the employed classes, retirement on State pension means a bare subsistence only, and, although supplementary payments may be claimed from other sources, many of these people of an independent character do not wish to obtain what they consider is charity. They consequently remain at work, even although the task is at times beyond their strength. I have often asked these people what they would really like to be done for them, and their reply is—a sheltered shop for the older men, where the tempo of work would be slowed down, where they could work shorter hours, draw their State pensions, and accept a reduced wage packet. They would still be in familiar surroundings; they would still see familiar faces; and, above all, they would still feel they "belonged" and were useful members of society within their own capacity.

We already have rehabilitation centres where the injured or sick worker is treated with special care and interest. Surely it is not too much to ask that the ageing worker, the faithful servant, should be given similar consideration, either in his old firm if it is big enough, or in some geriatric centre which might require an initial subsidy but which could quickly become self-supporting. Difficulties may arise with the trade unions, who fear dilutee labour and reduction of minimum wages, but if all concerned—the Government, the unions, the employers, and the old folks—would get together and produce a scheme which is economically practical, a vast number of old people would be freed from the fear of enforced idleness and could still contribute their quota to the productivity of the country.

In Glasgow there exists a rather unique institution known as the Guild of Aid. Its primary object is to help people, and particularly old people, to help themselves. They have an employment centre where old people from 65 to 80 are taught to use knitting- and weaving-machines and instructed in rug-making. Through lack of accommodation, only 22 can be employed, and they work for four hours daily, three days a week, and earn about 15s. to £1 a week. The finished products have a ready sale and a high standard of workmanship is guaranteed. The happiness, improved health, and quiet contentment of these old men and women, who, in the late sixties, have been instructed in a new and rather technical job, is an inspiration to all who are associated with the Guild, and, what is really important, the workshop is entirely self-supporting. I commend this project to any of you who are doubtful about the ability of old dogs to learn new tricks.

Unhappiness in the Aged

In general practice one has to be something of a psychologist, and for many years I have tried to get at the root cause of the despondency and unhappiness one finds in the aged. I am sure that the chief problem with which they are worried is the feeling of unwantedness—the sense of having no vocation, no real place in the community; no feeling that they are needed by and belong to someone. It is for that reason that I stress the tremendous importance of providing for these people some kind of remunerative job to make them feel that they are useful members of the community, and not, as so many of them feel, parasites on society. The next demon we must try to exorcize for the elderly is loneliness. In the census of 1951 it was found that nearly 250,000 people over 60 were living alone. There are in Britain over 3,600 clubs under the aegis of voluntary and paid social workers—Darby and Joan clubs, Evergreen clubs, Hobby clubs—but, despite the invaluable work these do, many elderly persons are housebound. In Glasgow there are 10,000 of them who lead very lonely lives. From the doctor's angle, old men are the greatest problem. They take little interest in their homes, which soon become squalid and dirty. They themselves take little care in their personal hygiene and become untidy, unshaven, and even unwashed. They become undernourished and dyspeptic because they do not bother to cook. For them the clock just ticks away the empty hours in an empty day.

It becomes almost essential to accommodate them in a home or hostel, but unless they are given some work to do they still remain crotchety, querulous, and despondent.

Fear is a demon that, at one time or another, haunts nearly every old person—fear of ill-health, fear of poverty, fear of insecurity, fear of friendlessness. These sorts of fears perhaps affect all of us at times, but they are accentuated by the increasing feebleness which accompanies senescence. Friendly and regular contacts by the health visitor and welfare worker, and more especially a call from the family doctor, help to maintain their morale and assume an importance and value in the mind of the patient that far outweighs the sacrifice of time entailed.

Housing

The housing of the ambulant aged is one of our major problems in the Welfare State. In 1948 the Enactment of 1845, which placed on children the duty to maintain their parents, was repealed, and now many families repudiate all responsibility for the care of their aged relatives. Most doctors agree that these old people are more happy and contented in their own homes than in an institution, but, for various reasons, accommodation cannot be provided for them. Their houses may be too large or may be situated in the upper flats of a block of flats, or a growing family makes it impossible for their relatives to house them. Hostels and eventide homes have been provided by the local authorities and by charitable organizations, but these, in general, constitute a very heavy burden on the taxpayer.

The Local Authority Homes in Glasgow involve a capital expenditure of £1,000 per pensioner and a weekly maintenance cost of from £6 to £9 per person. These hostels are beautifully furnished and generously staffed. All the domestic duties are undertaken by the staff, and the old people who dwell in these gilded cages are uprooted entirely from their old environment to spend the evening of their days in what Bernard Shaw describes as "the horror of the perpetual holiday." There is need for much less pretentious accommodation. The State, when spending the taxpayers' money, seldom considers economy. The Guild of Aid, about whose pensioners' workshop I have already told you, provides unpretentious accommodation, but, having no national exchequer behind it, does this within its income, yet rendering adequate service. It provides accommodation for some 60 people, varying in age from 65 to 80, in converted houses. Each pensioner has his or her own room, to which they bring their own furniture. They are provided with gas, electricity, and hot water. They can obtain help from a caretaker or voluntary worker for slight illnesses. They do their own housework and they purchase their own food. For these rooms the capital expenditure has been about £150, and the weekly rental is 12s. 6d. The old folks are happy and contented. They have some work to do and they have a feeling of good neighbourliness towards one another. To live wholly without responsibilities, as do those in the local authority hostels, often causes mental inertia and depression and physical degeneration.

Diet and Clothing

How often are we asked by our old patients or their relatives—What shall we eat, what shall we drink, and wherewithal shall we be clothed? For many old people the zest of eating is one of their chief remaining pleasures, and it is disappointing to have to tell them that an excess of food gives them no extra energy and, indeed, unduly taxes their digestive powers. A diet giving 1,800 to 2,000 calories is ample, and the aged should always be warned that obesity is a menace. For those in good health an ordinary mixed diet is all that is necessary, with perhaps the addition of extra sugar or sweets to restore flagging energy. The moderate use of alcohol in the aged I have found to do no harm, and a little wine for the stomach's sake will assist the secretion of flagging digestive juices, whilst the nightcap may often relieve anxiety and induce sleep.

All too often the elderly wear too many clothes which are so tightly buttoned that they restrict their joint movements and obstruct the circulation. Warm but loose-fitting garments should be recommended. Exercise is necessary to maintain health and should be regular and not spasmodic. Moderation in all things is a dictum that should never be forgotten, and a pleasant friendly round of golf or a few hours on a loch with a fishing-rod can still bring solace even to the octogenarian, and if these joys are beyond his means a regular walk each day may suffice. One of the most contented of my own old patients gave as the reason for his contentment, "I always put on my boots every morning."

Clinical Problems

May we now turn to some of the clinical problems that confront us in general practice? One of these is the care of those who have become so feeble either mentally or physically that they require constant skilled attention. Fortunately, this group does not constitute more than 2% of our pensioners. Cerebral deterioration, with its attendant sequelae, is the most common reason for hospitalization. Mental deterioration frequently comes on quite suddenly after some seemingly trivial accident or emotional upset. The old persons become forgetful and confused, and quickly progress to hostility to their relatives and even to delusions of persecution. They become depressed and melancholy and lose sense of time and place. With the best will in the world these people are very difficult to retain at home, and they require admission to an institution, which should be a long-stay annexe rather than a mental hospital. Drugs have little effect on their symptoms, but after some months under skilled supervision many of them improve.

What has been the pathology of their symptoms? It has been suggested that a succession of small shocks, each in itself so transient as to be unobserved but causing gradual but progressive deterioration, may be the predisposing cause. Research into the cause is necessary. Why should two people, each with somewhat similar physical characteristics, vary so much—one maintaining his full powers and the other undergoing gross mental deterioration? Both show a diastolic pressure over 110, but why the one should remain in full mental and physical vigour whilst the other becomes a senile dement is very difficult to appreciate and might form an interesting field of research. Is there perhaps some endocrine or blood factor involved?

Hemiplegics very frequently require hospitalization. If this can be obtained soon after the onset of the lesion, a surprising degree of recovery takes place. Formerly, one tended to let these patients lie in bed at home and regard the future as being completely in the hands of God or Nature, but now bed rest is superseded by exercise and physiotherapy. The patient is quickly introduced to a Bonaped walking-machine, and from there progresses to a tripod walking-stick. In a few months many are walking around the ward with comparative freedom. During 1954, from a geriatric unit in Glasgow, 60 out of about 200 such patients were discharged home able to live a reasonably normal life. A factor which has proved of great benefit to these hemiplegics is an unpolished floor treated with spindle-wood oil at frequent intervals. To persuade a hospital matron to agree to an unpolished floor requires much tact, but the confidence shown by the patients in walking on a non-slippery surface quickly convinced those in authority that appearance might be sacrificed to comfort and efficiency.

In practice one finds that incontinence, which may be present with both the hemiplegics and the mental cases, is the one single symptom which causes greatest difficulty to relatives. The first essential is to establish the cause of the incontinence. If it has an organic base treatment may prove helpful, but if it is of senile origin drugs are of no real value. Limitation of fluids, regular use of urinals, and keeping the patient ambulant all help. For men a rubber urine-container solves the problem, but, unfortunately, the

female anatomy has been so designed that our instrument makers have not succeeded in devising any apparatus that can cope with incontinence. Faecal incontinence is often due to impacted faeces, when just a thin trickle gets past the mass. Enemas solve this problem and give much encouragement to both patients and relatives. Try to avoid colostomies in the aged. With the intelligent patient all goes well, but with the uneducated infection of the surrounding skin causes much discomfort and misery.

Severe rheumatoid or osteoarthritic cases are not common in the real old-age group. Death brings relief from their misery at an earlier age.

Cancer is not a common cause of death in the aged. Many of them die with cancer but not of cancer. The neoplasm seems to grow very slowly in the aged, and its virulence is much reduced.

Congestive heart failure is very common in ambulant elderly patients. They respond very well to bed rest and treatment with digitalis, mersalyl, and aminophylline. Many of them develop coronary disease, but this manifests itself often only by a little breathlessness, and seldom causes acute pain. An E.C.G. is diagnostic. Within three to four weeks the lesion seems to heal satisfactorily and they can be allowed up very much more quickly than the patient in his fifties.

In the respiratory diseases, pneumonia has long since lost the title of "captain of the men of death." The antibiotics have controlled the ravages of that disease, and it is seldom now that one sees a case of textbook pneumonia, but influenzal and virus pneumonias still take their toll.

Foot defects cause much distress to the elderly, and it is estimated that almost 10% of those who are housebound are crippled by corns, callouses, bunions, and flat-feet. The provision of an adequate chiropody service would bring much comfort to the sufferers and would enable them to lead once again a useful and independent life.

Ferguson, a general practitioner in Paisley, observed, over 25 years, the incidence and cause of death of 280 patients in his own practice who were over the age of 70. He chose that age because they had escaped the pitfalls which engulf the middle-aged and because it was the classical conception of the allotted span. He found that 33 men and 57 women —32% of the whole—died from what he called normal senescence without any obvious active disease, "God's finger touched them and they slept." No post-mortem examinations were done, but it would have been of real interest to know what particular part in the most intricate machine ever designed—the human body—had worn out, and whether with more specialized knowledge life could have been usefully sustained for a further period.

Conclusion

What I have said may perhaps focus attention on the fact that the study of the ageing and the aged is not a hopeless and rather useless sphere of medicine. The primary function of the practitioner should not be to add to longevity but to prevent and curtail incapacity—not to add years to life but to add life to years. Research work could be undertaken by close association between general practitioners, geriatricians, and laboratory workers into such subjects as the onset of mental confusions, incontinence, and hemiplegia; are they solely due to arterial degeneration or do other factors play a part? Obesity in old women—what is the predisposing factor?

To a large extent we have conquered microbic diseases. Virus infections are gradually coming under control. We must now mobilize our resources and energies to combat the degenerative diseases, and much may be learned in that field by a close study of our ageing population.

THE ACUTE ABDOMEN IN THE AGED

BY

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This paper reviews 120 personal cases of acute abdominal emergency, excluding acute retention of urine, in patients over the age of 70. The choice of 70 years as the lower age limit is an arbitrary one, for, as is well known, some patients "wear" better than others, and the age in years is no accurate guide to the state of the tissues. Nevertheless, at this age most people have given up active work, and it is considered worth while to review the results of surgery to prolong happily a well-earned retirement threatened by sudden disaster. Several papers devoted to the surgery of old age have appeared in recent years, but none makes more than passing mention of emergencies. Childs and Mason (1949), for example, include 15 emergencies in their series of 99 cases over the age of 70 years, but do not discuss them separately.

Analysis of Results

This series is a consecutive one, and no case, however unpromising it appeared on admission, has been excluded. The mortality rate includes all patients who died in hospital, and all survivors were ambulant on discharge. The total number of cases and the mortality rates for the various conditions are arranged in five-year age groups in Table I,

TABLE I.—*Mortality According to Age and Condition*

	Age:	70–74	75–79	80–84	85–89	90+	Total
Intestinal obstn.	Cases	5	13	9	2	1	30
	Deaths	4	4	4	1	0	13
Strang. hernia	Cases	16	21	11	5	1	54
	Deaths	2	5	0	1	0	8
Perf. peptic ulcer	Cases	3	3	1	—	—	7
	Deaths	1	0	0	—	—	1
Acute appendicitis	Cases	7	5	3	—	—	15
	Deaths	1	0	2	—	—	3
Perf. colon	Cases	1	3	3	—	—	7
	Deaths	1	2	2	—	—	5
Miscellaneous	Cases	1	1	5	—	—	7
	Deaths	0	0	2	—	—	2
Total	Cases	33	46	32	7	2	120
	Deaths	9	11	10	2	0	32

which shows clearly that intestinal obstruction is by far the commonest acute surgical condition in old age and also bears a heavy mortality. There emerges also, rather surprisingly, the fact that age *per se* does not influence the mortality in operations for acute abdominal emergencies in the elderly. The total mortality of 26.7% is of the same order as the 33.5% of Owen and Murphy (1952), which included some cases of acute retention of urine, and the 32.1% recorded by Carp (1950).

Strangulated Hernia

The results in these cases are further analysed in Table II. Interesting clinical features here were the relatively high incidence of femoral hernia in old men, and the finding of the vermiform appendix, strangulated and gangrenous, in one femoral and two inguinal sacs. One

TABLE II.—*Strangulated Herniae*

	Males	Females	Total	Resection of Intestine	Bowel Invaginated	Deaths
Inguinal	19	3	22	3	0	1
Femoral	6	23	29	4	8	5
Umbilical	1	1	2	0	0	2
Incisional	0	1	1	0	0	0

femoral hernia was diagnosed only at laparotomy for small intestinal obstruction, when a loop of bowel was found just entering the femoral canal on the left side as a Richter's hernia. Even knowing it to be present, and under full anaesthesia, it was still not possible to feel this hernia through the fat of the groin. Richter's hernia was, in fact, very common in the femoral cases.

Approximately half of these hernia cases were admitted to hospital 24 hours or less after the onset of strangulation, a measure of the patient's alarm (contrast with other obstructions) and the ease of diagnosis. Nevertheless, and particularly in cases of Richter's hernia, the delay in admission was sometimes considerable, being seven days in one case, six days in three, five days in three, and four days in two cases. The fatal cases are shown in Table III.

TABLE III.—*Analysis of Deaths in Strangulated Hernia*

Sex and Age	Type	Length of History	Condition of Bowel	Time of Death	Cause of Death
F 76	Femoral	30 hours	Gangrenous—resected	2nd day	Pulmonary oedema
F 79	,,	24 ,,	,,	2nd ,,	Bronchopneumonia
M 72	Inguinal	48 ,,	Considered viable	5th ,,	Perforation of ileum
F 79	Femoral	4 days	Viable	24 hours	Massive collapse lung
M 75	,,	3 ,,	Gangrenous—resected	4th day	Paralytic ileus
F 89	,,	6 ,,	Gangrenous—oversewn	12 hours	Obstruction
F 75	Umbilical	6 ,,	Gangrenous—8 feet	4 ,,	Unfit for resection
M 73	,,	24 hours	Viable	7th day	Pulmonary embolus

Other Causes of Obstruction

These cases are summarized in Table IV, and, as expected, the largest single cause in this group was carcinoma of the colon. Surprisingly, adhesions were responsible in an equal

TABLE IV.—*Other Causes of Obstruction*

Cause	Cases	Deaths
Carcinoma colon	13	5
Adhesions	11	5
Gallstone, ileus	1	1
Volvulus small intestine	2	2
,, sigmoid colon	2	0
Spastic ileus	1	0

number, for the two cases of small-gut volvulus were due primarily to adhesions. The cause of the adhesions was post-operative in eight cases and a calcified tuberculous mesenteric gland in one; no cause could be traced in the remainder.

The average length of history was 3½ days in small-gut obstructions (range, 12 hours to 6 days) and 4½ days in the large-gut cases (range, 1 to 12 days), suggesting both the complacency of the patient before seeking medical aid and the difficulty in diagnosing the presence of mechanical obstruction.

An analysis of the 13 deaths shows that the abdominal condition was directly responsible for the fatal issue in seven cases and indirectly so in one (pulmonary embolism). Two patients died from congestive heart failure, present on admission, on the 7th and 28th post-operative day respectively; two more died of cerebral thrombosis (7th and 10th days); and the thirteenth case, a female, of haemorrhagic cystitis due to a self-retaining catheter employed for incontinence of urine. One patient with perforation of the colon above a carcinoma survived after laparotomy, colostomy, and drainage of the area.

Perforated Peptic Ulcer

There were seven cases of perforated peptic ulcer (six duodenal and one gastric), with one death on the fourth post-operative day. In this case the liver was found to be replaced almost completely by deposits of carcinoma, though no primary growth was discovered in the abdomen. Post-mortem examination showed it to be in the bronchus with no gross pulmonary collapse. The other six patients made uneventful recoveries and were all well when seen later in the out-patient department.

One old gentleman, operated on in 1952 at the age of 80, had been operated upon in 1945 and 1948 for perforated duodenal ulcers and had survived a haematemesis in 1949. At operation most of the anterior wall of the proximal duodenum was found to have sloughed, leaving a hole 3 by 7 cm. This was closed by suture, and a posterior gastro-jejunostomy performed. He was readmitted in 1954 with an attack of severe abdominal pain, but otherwise was still hale and hearty. His symptoms quickly subsided, and a barium meal showed the gastro-jejunostomy to be functioning, with no evidence of anastomic ulcer. The stomach was also emptying in part through the pylorus.

Three of these patients were seriously ill on admission, with grunting inadequate respiration, cyanosis, and rapid low-pressure pulse. Nevertheless it was decided that the only chance of survival lay in operation, and it was remarkable how the respiration and the heart, with its burden thus lightened, improved at once when the abdomen was opened and the irritant fluid sucked out. None gave rise to any further anxiety.

Acute Appendicitis

Acute appendicitis is said to be rare in the elderly, but in this series there were 15 cases, all treated by operation, with 3 deaths. In 10 cases the appendix was gangrenous and in 6 diffuse peritonitis was present. It is interesting to note that no fewer than 10 of these 14 cases were diagnosed correctly and sent to hospital within 48 hours of the onset of symptoms. In only one case was diagnosis unduly delayed. A woman of 83 was admitted on the seventh day of symptoms with an obvious diffuse peritonitis and peripheral circulatory failure. She had complained of epigastric pain for seven days and had vomited once daily for six days. At operation the peritoneal cavity was full of pus, and she died four days later. The second death was due to bronchopneumonia on the 13th day, and the remaining one from peritonitis on the 3rd day. In this last case the appendix had sloughed and the pelvis was full of fluid faeces from the caecum.

Perforations of the Colon

These cases are summarized in Table V. In all the sigmoid perforations solid faeces had to be removed from the pelvis, and the cause of the perforation was not identified with certainty. There was no evidence of carcinoma, and presumably a diverticulitis or stercoral ulcer was the initial lesion.

TABLE V.—*Perforations of Colon*

Sex and Age	Site	Time of Death	Cause of Death
M 83	Sigmoid	6 hours	Peritonitis
F 84	Caecum	Survived	
M 82	Carcinoma caecum	4th day	Peritonitis
M 71	Sigmoid	5th ,,	,,
F 76	,,	4th ,,	,,
M 75	,,	6th ,,	Bronchopneumonia
F 79	,,	Survived	

Problems of Diagnosis

General

In the accurate diagnosis of the acute abdomen, particularly in the later stages when widespread pathological changes obscure the earlier localizing signs, a clear and chronological account of the symptoms is of the utmost value, and it is just this information which is most difficult to obtain from old people. Not infrequently on admission they are becoming worn out from an illness of several days' duration; cerebration and memory, particularly for recent events, are failing from age and toxaemia; the will to live is fast fading; and deafness may be an additional handicap. The patient's halting story is at variance with the information in the doctor's letter, especially with regard to times of

events. It has proved well worth while to take a history from a relative also, preferably a daughter or daughter-in-law who has been nursing the patient, and in the latter half of the series this has been done whenever possible. A second difficulty is that these patients appear much less sensitive to pain than the average adult, though naturally there is marked individual variation, and frequently they are unable to distinguish between the various types of pain. Thirdly, there is a marked tendency among the elderly to attribute any abdominal pain to "indigestion" or to constipation, which leads to delay in seeking advice and initiates some of the difficulties mentioned above. Abdominal signs, on the contrary, are nearly always present, and, if interpreted with due regard for the condition of the individual patient, usually will lead one to the correct diagnosis. In peritonitis, for example, one cannot expect the same degree of rigidity in an old lady as in a muscular young man.

Intestinal Obstruction

Little need be said on the diagnosis of strangulated hernia, for with the exception of the case already mentioned it was quite straightforward. Vomiting, however, is not an invariable accompaniment of trapped bowel. Particularly is this so in hernia of the Richter type (in this series it was absent in 12 of the 49 cases of strangulated intestine), and if a known hernia has become enlarged and painful, or if an irreducible hernia has appeared, the only safe course is to regard it as a strangulation.

The diagnosis of mechanical obstruction, on the other hand, can be extremely difficult, particularly in cases of carcinoma of the colon, where acute is superimposed on chronic obstruction. Little or no importance should be attached to the patient's statement of the last bowel action, for not only is memory unreliable, but many of these old people cease to open their bowels at all regularly, even to the point of faecal impaction, and, conversely, complete obstruction can be followed by one or more acts of defaecation. Fortunately, however, not only is the passage of flatus, or the absence thereof, of more value in diagnosis, but it is the one observation which does impress itself on the mind of the elderly. "Look to the wind and the water" was the advice of a wise old man to a newly qualified doctor.

Vomiting tends to be less marked in the elderly, is not infrequently absent in large-gut obstructions (nearly always if the ileo-caecal valve holds), and may be absent in small-gut obstruction, as in two cases in this series—a volvulus of three days' duration with 6 feet (1.8 m.) of gangrenous ileum, and a band adhesion of 12 hours' duration. Thus, with the gross distension often present when the patient is admitted, diagnosis of the site of obstruction may be impossible on clinical grounds. If any doubt existed, *x*-ray films of the abdomen were taken in supine, erect, and lateral positions. These proved most helpful, but were not infallible. For example, a grossly distended caecum in one case was mistaken for a volvulus of the sigmoid loop by both surgeon and radiologist independently.

Perforations and Appendicitis

Of the seven perforated peptic ulcer cases four presented the typical clinical features of this condition, but the remaining three patients complained only of sudden severe pain in the right iliac fossa. This atypical presentation can be most confusing; for, in the elderly, acute appendicitis sometimes presents in exactly the same way, and in both of these conditions signs are limited to the right side of the abdomen. Usually in such a case of appendicitis the appendix is found to be perforated, and one must presume that the patient has attributed the preliminary less severe pain to indigestion or constipation, and has forgotten it in his subsequent agony. Despite the most careful consideration of the evidence two cases of perforation were diagnosed pre-operatively as appendicitis with peritonitis, and one case of appendicitis as a perforated peptic ulcer. The remaining 18 cases were all diagnosed correctly.

Of the seven large-bowel perforations four were diagnosed correctly, one as a perforated peptic ulcer, and two as perforated appendices. In the latter two cases the summit of the sigmoid loop was found in the R.I.F. and the perforation was in this region. In this condition a short history, and signs of peritonitis which are diffuse but maximal in the lower abdomen, suggest the diagnosis.

Miscellaneous

Two of these cases—a retrocaecal haematoma and an acute inflammation of a solitary diverticulum of the caecum—were misdiagnosed as acute appendicitis. Post-operative review of the history and signs produced no further information which might have made the diagnosis doubtful—understandably so in the latter case.

TABLE VI.—*Miscellaneous Cases*

Sex and Age	Diagnosis	Remarks
F 82	Retroperitoneal haematoma	Cause unknown. Died 9th week
F 83	Abscess L.I.F.	Diverticulitis. Drained. Recovery
F 84	Acute cholecystitis	Cholecystostomy. Stones removed. Recovery
M 81	Perforated gall-bladder	Suture and drainage. Died 9th day. Pulm. emb.
F 75	Acute pancreatitis	Diagnosed at laparotomy. Abdomen closed. Recovery
M 80	Acute diverticulitis caecum	Invaginated. Recovery
F 73	Internal haemorrhage	Diagnosed at laparotomy. Recovery

The case of intraperitoneal haemorrhage was diagnosed as acute appendicitis with diffuse peritonitis. This patient gave a history of intermittent abdominal pain for 15 days, described as indigestion, and of severe pain in the R.I.F. for 24 hours following a large dose of cascara the previous day. She had vomited twice on the day of admission, was pyrexial, and showed all the signs of peritonitis. Laparotomy revealed two pints (1.1 litres) of fluid heavily stained with old dark blood. No cause for this was found. The patient made an uneventful recovery and had had no further symptoms six months later.

Treatment

The general treatment of these old people presents many problems, for not only is the will to live often reduced but other bodily systems may be failing in addition to the stricken abdomen. Nutrition is often poor and a high-protein diet desirable, but it is far easier for the surgeon to order this than for the nursing staff to ensure that the patient complies. Similarly, thirst loses its insistence, and drinking is regarded as an unmitigated nuisance. Nevertheless, the renal function is often below par, concentrating power reduced, and the *volume obligatoire* correspondingly increased in patients suffering to a greater or less extent from dehydration. For these reasons no hesitation was felt in maintaining, for days if necessary, the intravenous infusion of 5% dextrose in water or of 4.3% dextrose in 0.18% saline, according to circumstances. In general, water is not retained without salt, and only occasionally was there any concern for the chest. Unless thought to be grossly abnormal, the serum chemistry was left to correct itself in due course by adding salt to the diet; pre-operatively, the urinary chlorides were estimated by the Fantus test and the serum chlorides determined if thought necessary, and intravenous normal saline was given when indicated. If nutrition was poor blood or "casydrol" was also given intravenously after correcting the fluid balance. Once the emergency was over it fell to the nursing staff to bully the patients into eating and drinking the necessary quantities. Extra protein can be supplied in the form of "casilan," but the patients readily detected its presence in any food or drink and found it unpalatable.

These patients were not forced from their beds in the first few post-operative days, but the subject was broached to them, and any desire to get up was enthusiastically encouraged. Routine breathing exercises and limb move-

ments under the supervision of a physiotherapist were, however, started on the first day, and the patients got out of their beds, irrespective of their feelings, when considered fit to do so. Other geriatric problems are beyond the scope of this paper.

Operation in these old people should not be delayed for more than an hour or two for resuscitation and correction of fluid balance. Ageing tissues lose their powers of compensation and their resistance to infection (peritonitis is much more common than abscess formation in acute appendicitis), the pathological process has usually been active for many hours before admission, and further delay may tip the scales against recovery. In cases of doubt it is safer to operate than to observe, for these patients are "tougher" than they look and withstand operation well provided it is performed quickly, and, as a corollary, only the minimum necessary is done. Not one of these patients was considered unfit for operation, and local analgesia was used only for three of those with strangulated herniae. All other patients were anaesthetized with cyclopropane, with or without a relaxant drug.

In the strangulated herniae, areas of bowel, gangrenous or of doubtful viability, were invaginated where possible in preference to resection. As Owen and Murphy also found, this procedure is quicker and safer and is not followed by obstruction due to stricture. Undoubtedly it saved several lives, for the mortality of resection at this age is high.

For intestinal obstruction a laparotomy was performed rather than a blind decompression operation, for the following reasons. First, the clinical diagnosis of site and of cause of obstruction is not infrequently impossible, and *x*-ray investigation is not infallible. Even a confident diagnosis of obstruction due to carcinoma of the colon has been proved wrong at laparotomy. Secondly, in cases of carcinoma one can form an opinion on the possibility of a second operation to remove the growth (as opposed to attempted cure), for it is my belief that in some cases, even if secondary deposits are present, removal is worth while to get rid of the colostomy. If so, it is better to place the colostomy where it will be removed with the growth and thus save a third operation for its closure: if not, the decompression colostomy can be sited at the best possible place for its secondary role as an artificial anus. Finally a caecostomy causes so much distress to old people that it can rarely be justified as a blind or as a planned procedure. Ileo-transverse colostomy is usually a much more desirable operation except when the ileo-caecal valve is competent and one is therefore dealing with a closed-loop obstruction. The future is short for these cases, and we should make it as comfortable as possible as quickly as possible rather than perform lengthier procedures of academic accuracy.

In general, old people are intolerant of intragastric tubes, and in such cases there is less upset to the patient in the post-operative period if the tube is passed twice a day and removed as soon as the aspiration is completed. Theoretically, this is not so efficient as continuous suction, but in practice the results are better, owing to the greater mental and therefore physical rest of the patient.

The perforated peptic ulcers were treated by early operation, closure of the perforation, and removal by suction of all fluid from the peritoneal cavity. It is surprising how much can be thus removed from the pelvis and from above the liver—2 pints (1.1 litres) is not unusual—and literally amazing to see the improvement in the patient when this is done. Drainage of the operative area or pelvis was not employed in any of these cases and there were no complications.

The acute appendices were treated on similar lines, care being taken to remove all exudate, but in most of these cases a drain was put down to the appendix bed. Of the survivors, one developed a pelvic abscess, which was subsequently drained.

Of the miscellaneous group, the retroperitoneal haematoma was evacuated and drained. This may have been a mistake, for in the only other example of this condition which I have seen death also occurred following drainage. Martin (1949) also quotes the high mortality of such interference, and probably it is better to remove the blood and to close the wound, for these cases usually come to operation misdiagnosed as acute appendicitis.

Perforations of the sigmoid were treated by cleansing of the peritoneum, closure of the perforation, left iliac colostomy, and a course of antibiotics. The condition proved to have a much higher mortality in old than in middle age.

Summary and Conclusions

A review has been made of 120 personal cases of the acute abdomen, excluding acute retention of urine, in patients over the age of 70 years.

The conclusion reached is that elderly people with acute abdominal emergency conditions withstand operation remarkably well, despite the presence of chronic lesions elsewhere, provided there is no undue delay in reaching the theatre and that the minimal intervention necessary is quickly carried out.

In the elderly, age itself has no effect on the mortality rate, and in cases of doubt it is usually safer to operate than to observe.

Every effort should be made to reach an accurate diagnosis on clinical grounds and no more than an hour or two spent on investigation and resuscitation. Procrastination is the thief not only of time but of the patient's remaining days.

I am greatly indebted to the consultant surgeons of the Brighton and Lewes Hospital Group for permission to treat these patients.

REFERENCES

Carp, L. (1950). *British Medical Journal*, **2**, 1198.
Childs, P., and Mason, S. A. (1949). Ibid., **2**, 1389.
Martin, K. W. (1949). Ibid., **1**, 1118.
Owen, R. A. C., and Murphy, A. F. (1952). Ibid., **2**, 186.

THE AETIOLOGY OF POST-PARTUM HAEMORRHAGE

BY

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Post-partum haemorrhage as a cause of maternal mortality has assumed more prominence of recent years owing to the reduction in deaths from other causes. In an attempt to evaluate the aetiological factors concerned, the details of patients delivered in the Obstetric Unit of the London Hospital were analysed. This report is concerned with the 2,444 successive vaginal deliveries in the years 1950–2.

Brews (1953) deals with the causation of post-partum haemorrhage under three headings: (1) failure of contraction and retraction of the uterine muscle owing to inertia or exhaustion; (2) the presence in the uterus of some mechanical obstruction to retraction such as partial abnormal adherence of the placenta, or the retention of a cotyledon; and (3) deficiencies of blood coagulability. Under the first heading are included overdistension (twins and hydramnios), prolonged labour, prolonged anaesthesia and analgesia, antepartum haemorrhage, precipitate labour, retention of

urine, and nervous shock. To these Theobald (1950) adds anaemia, blood dyscrasias, and insomnia towards the end of pregnancy. Multiparity, especially if the pregnancies have followed each other in rapid succession, and the presence of fibromyomata and concurrent debilitating diseases have also been suggested. Possibly the commonest cause of an excess loss is one to which no unit would admit—namely, mismanagement of the third stage of labour.

Present Investigation

At the London Hospital most of the normal deliveries are conducted by medical students under the supervision of the midwives and residents. Particular care is taken to collect as much as possible of the post-partum blood loss, and a generous estimate is made of the amount that escapes collection. A loss of 20 fl. oz. (570 ml.) or more is regarded as a post-partum haemorrhage. In the years under review it was not the practice to administer ergometrine before delivery of the placenta.

In this series of 2,444 patients there were 405 with a post-partum haemorrhage—an overall incidence of 16.5% (Table I). Prolonged labour and operative delivery under anaesthesia were not infrequently associated, but for the patients delivered by forceps, the majority under general anaesthesia, there was a post-partum haemorrhage rate of 19.6%. Labours prolonged more than 30 hours were associated with a rate of 21.7%, which must be compared with the figure of 16.2%, the rate for labours of less than 30 hours' duration. After a forceps delivery the collection of blood lost is often incomplete, and in all probability these figures are underestimates and therefore the importance of the three aetiological factors—prolonged labour, operative delivery, and anaesthesia—is even greater than the figures would suggest.

TABLE I

	No. of Patients	No. with P.P.H.	% Incidence
Whole series	2,444	405	16·5
Prolonged labour	147	32	21·7
Operative delivery with anaesthesia	289	57	19·6
Multiple pregnancies	60	9	15·0
Ante-partum haemorrhage	81	8	8·7
Hydramnios	19	1	5·2

Overdistension of the uterus was not associated in this series with any increased incidence of haemorrhage. There were 60 patients with twin pregnancies, and the incidence of haemorrhage was 15%. The majority were admitted for rest during the antenatal period and began labour often more rested than those patients with single pregnancies, and this may have offset the effect of the distension. Patients with a clinical diagnosis of hydramnios did not receive this period of rest; 19 pregnancies were so complicated; only one suffered from a post-partum haemorrhage.

Patients with ante-partum haemorrhage were managed conservatively and, excepting cases of marginal or more centrally placed placenta praevia, a vaginal delivery was allowed. Eighty-one patients came into this group, eight having a subsequent post-partum haemorrhage.

Of the 405 patients who bled excessively, 243 were primigravidae and 162 were multigravidae, a ratio of 3:2. This is the normal ratio of admission to the unit; for instance, in 1953 there were 543 primigravidae and 370 multigravidae.

The accurate diagnosis of fibroids in association with pregnancy is difficult. Fibroids were diagnosed on a number of occasions, but in only one pregnancy were they thought to be responsible for the haemorrhage; this was in a patient who had a submucous fibroid which caused a loss persistent enough to necessitate a hysterectomy.

No case of afibrinogenaemia was diagnosed, but two patients, each of whom was delivered of a stillborn macerated foetus, had severe haemorrhage.

Manual removal of the placenta was performed for delay of more than one hour in the third stage, for haemorrhage not controlled by simpler methods, and occasionally as a prophylactic measure following a forceps delivery. There were 13 occasions when haemorrhage was not the indication; in half the remainder the blood loss was severe. The total number was 61.

If 40 fl. oz. (1,140 ml.) is taken as a severe loss, then 83 patients suffered a severe post-partum haemorrhage (Table II); of these, 49 were primigravidae and 34 multigravidae—the same 3:2 ratio as for the larger groups.

TABLE II.—*Volume of Loss*

Over 40 oz. (1,140 ml.), but exact loss not recorded	3
40– oz. (1,140– ml.)	39
50– ,, (1,420– ,,)	15
60– ,, (1,700– ,,)	14
70– ,, (1,990– ,,)	4
80– ,, (2,270– ,,)	7
90 oz. (2,570 ml.) or over	1
	83

Of the 34 multigravidae, 14 gave a history of third-stage complications in a previous labour (Table III). These complications were either an excess loss, sufficient for the patient to know that it was excessive, or a manual removal of the placenta. An attempt was made to discover the subsequent history of these and the other patients in the group. Information was obtained from some 60%. Twenty of the multiparae were followed; 4 had had further pregnancies, and 3 again experienced a complication. Twenty-nine primiparae were followed; 11 had had subsequent pregnancies and 6 had had further difficulty.

TABLE III

	No.	Previous History of Complicated Third Stage	Followed Up	Subsequent Pregnancy	Subsequent Difficulty
Primigravidae	49	—	29	11	6
Multigravidae	34	14	20	4	3

Among those patients who lost over 40 oz. (1,140 ml.) there were 54 for whom details of two or more pregnancies were available. In 21, difficulty in the third stage was a recurrent complication—a rate of 38.9%. In this group the incidence of manual removal of the placenta was particularly high; 14 required a manual removal in one of their pregnancies, and 3 required the procedure on two occasions.

TABLE IV.—*Incidence of Manual Removal of the Placenta (3-Year Period)*

	No.	Manual Removal	%
Vaginal deliveries	2,444	61	2·5
Patients with P.P.H.	405	48	11·5
,, ,, severe P.P.H.	83	23	27·7
,, ,, recurrent difficulty	21	7	33·8

The figures shown in Table IV support the view that abnormal adherence of the placenta and consequent difficulty in the third stage may be a recurrent condition.

Conclusions

Prolonged labour, forceps delivery, and anaesthesia are important aetiological features in the production of post-partum haemorrhage.

Overdistension of the uterus as a factor has been over-emphasized.

Neither accidental nor unavoidable ante-partum haemorrhage predisposes to P.P.H.

Fibroids rarely cause haemorrhage, but when responsible the haemorrhage is severe.

Severe post-partum haemorrhage is apt to recur in subsequent pregnancies, and is possibly due to abnormal

adherence of the placenta. Previous post-partum haemorrhage should be an indication for hospital confinement.

I would like to record my thanks to Mr. Victor Lack, Mr. Alan Brews, and Mr. Robert Percival for their help in the preparation of this report, and also to Miss E. Green for her efforts in contacting the patients.

REFERENCES

Brews, A. (1953). In *Eden and Holland's Manual of Obstetrics*, 10th ed. Churchill, London.
Theobald, G. W. (1950). *British Medical Journal*, 1, 659.

ECOLID: A NEW HYPOTENSIVE AGENT

BY

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AND

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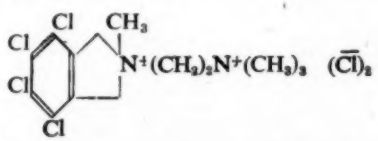
During the past five years ganglion-blocking agents have been used extensively in the treatment of arterial hypertension. The discovery of the activity of hexamethonium by Paton and Zaimis (1949) placed at our disposal an active therapeutic agent capable of producing a substantial reduction in the blood pressure. Subsequent research has been directed to the synthesis of new drugs offering advantages over hexamethonium.

In the treatment of hypertension, it is desirable to obtain a sustained fall in the blood pressure by the oral administration of a drug producing a minimum of side-effects. Hexamethonium is inconstant in action by mouth, its duration of action is short, and it produces side-effects characteristic of generalized ganglionic blockade. Maxwell and Campbell (1953) examined a number of methonium homologues and indicated the suitability of one of them, pentolinium, for therapeutic application. At present pentolinium is the most active hypotensive drug available and it has been widely employed. Trapold *et al.* (1955) have described the pharmacological actions of a new synthetic compound, "ecolid" (SU-3088), and Grimson *et al.* (1955) have demonstrated its activity in lowering the blood pressure in man.

Trapold *et al.* (1955) have described a series of halogenated isoindolines with potent ganglion-blocking activity of long duration. Ecolid was the most active compound investigated. It is 4,5,6,7-tetrachloro-2-(2-dimethyl-aminoethyl)-isoindoline dimethochloride, the structural formula being as follows:

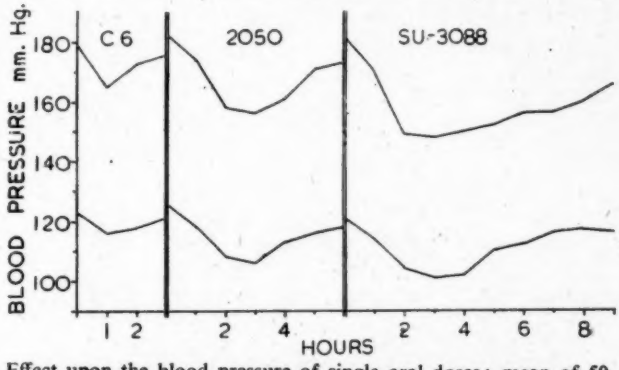


The chloride salt contains 83.45% active cation. In animal experiments it was found that this new compound is several times as active in parenteral dosage as hexamethonium, and twice as active as pentolinium. In oral dosage its activity is the same as pentolinium, but the duration of action is appreciably longer. Vagal activity is affected less than sympathetic. The relative shortness of the methylene chain is of interest. This suggests that the overall molecular length is of greater importance in obtaining a specific synaptic fit than the spacing between the quaternary nitrogen atoms.

Clinical Investigation

Twelve patients were selected who had severe hypertension and whose blood pressures remained high, despite admission to hospital and treatment by bed rest, sedation, and dietary and salt restriction. Five of these patients (Cases 1–5) had been treated previously with various ganglion-blocking agents for several years, and their readmission to hospital was considered necessary owing to the recurrence of hypertension during out-patient treatment. All the patients were investigated fully as described by Graham and Maxwell (1954). This series of patients formed a good test for a new ganglion-blocking agent, as the hypertension was severe in every case.

Ecolid was administered by mouth before breakfast, to facilitate absorption. During 85 observations it was found that the effective dose varied from 25 to 200 mg. In common with other ganglion-blocking agents, the response to the first dose was greater than that obtained subsequently, and higher dosage was required in those cases previously treated with sympathicolytics. In some cases a response was not obtained until the second or third day of treatment, suggesting a cumulative effect. A marked fall in blood pressure sometimes followed the initial dose of 25 mg. In every case adequate dosage produced a fall in blood pressure to the basal level, with increased peripheral blood flow as shown by a rise in temperature of the extremities, and postural hypotension. Evidence of vagal inhibition was present in the form of mydriasis, paralysis of accommodation, and dryness of the skin and mouth. Five barium examinations showed a variable depression of gastro-intestinal motility, this being marked after doses of over 150 mg. Postural syncope resembled that produced by pentolinium, loss of consciousness being slow and accompanied by nausea. The dose required to produce a marked fall in blood pressure was rather less than that of pentolinium, and the duration of action was approximately double. These results are compared with those from hexamethonium in the Chart.



Effect upon the blood pressure of single oral doses: mean of 50 observations upon each drug. C 6 = hexamethonium 250 mg.; 2050 = pentolinium 100 mg.; SU-3088 = ecolid 64 mg. Dosage in cation.

During the last four months ecolid has been used in the treatment of this series of 12 patients. It was found possible to lower the blood pressure to a satisfactory level in every case. The severity of the side-effects depended to some extent upon the dosage used. Mydriasis was a constant finding, and blurring of vision commonly occurred during initial treatment, but was less severe with maintenance dosage. Precautions were necessary to overcome development of constipation, and in three cases treatment had to be stopped owing to nausea and vomiting and obdurate constipation. A preference for pentolinium was expressed by two patients (Cases 2 and 5) who have had extensive experience of ganglion-blocking agents.

Bain *et al.* (1955) have shown that combination of reserpine with pentolinium enabled reduction in dosage of the latter and thereby a decrease in side-actions. Combined dosage of reserpine and ecolid was used in the maintenance treatment of Cases 7–12, reserpine, 2 mg. by mouth, being

given in the evening. Reduction in the maintenance dosage of ecolid was possible and side-effects were fewer. During the period of observation, tolerance to ecolid has not developed, and in some cases reduction of dosage has been possible. The response was good in eight cases and fair in one, the drug being stopped in the remaining three owing to severity of side-actions. These results are summarized in the Table.

Summary of Results of Treatment of 12 Patients with Severe Hypertension. Mean Blood Pressures when Recumbent are Recorded. Patients 7–12 Received Also 2 mg. Reserpine by Mouth at Night

Case No.	Sex and Age	Type of Hypertension	B.P. Before Treatment	B.P. During Treatment	Daily Dose of Ecolid	Side-effects	Result
1	F 38	Malignant	260/155	150/100	175 mg. b.d.	Unable to read. Slight dryness of mouth	Good
2	F 38	Malignant (toxaemia of pregnancy 3 years ago)	260/140	180/100	150 mg. b.d.	Blurring of vision. Moderate constipation	,,
3	M 41	Malignant	240/140	150/100	150 mg.	Blurring of vision. Severe constipation	Drug withdrawn
4	M 44	Malignant (acute nephritis 24 years ago)	250/140	145/100	200 ,,	Unable to read. Dryness of mouth and dry cough. Slight constipation	Fair
5	F 57	Essential, malignant phase	230/140	165/105	75 ,,	Nausea and vomiting. Constipation. Light-headedness	Drug withdrawn
6	M 53	Malignant	210/120	160/90	100 ,,	Blurring of vision	Good
7	F 57	Essential	215/150	150/95	75 ,, b.d.	Blurring of vision. Slight dryness of mouth	,,
8	M 61	,,	220/110	140/85	50 mg.	Slight dryness of mouth	,,
9	F 64	,,	220/120	160/70	25 ,,	Severe nausea and vomiting. Constipation	Drug withdrawn
10	F 57	,,	240/150	140/95	125 ,, b.d.	Slight dryness of mouth	Good
11	F 55	,,	220/140	135/90	125 mg. b.d.	Nil	,,
12	M 59	Essential, malignant phase	180/120	155/95	100 mg.	Blurring of vision	,,

Discussion

The introduction of ganglion-blocking agents in the treatment of hypertension is due to the work of Dale (1914), who described the properties of tetraethylammonium (T.E.A.). Recognizing the improvement which could be obtained by surgical procedures in patients with severe hypertension, Lyons *et al.* (1947) employed T.E.A. to reproduce the effect of sympathectomy. The need for such a drug was demonstrated by the extensive use of T.E.A. in intravenous dosage, despite its marked toxicity. Organe *et al.* (1949) showed that the bis-quaternary amine hexamethonium was a practical method of lowering the blood pressure. However, the generalized activity of this drug proved to be a handicap, as its actions, beyond inhibition of sympathetic ganglia, constituted side-effects. The serious complication of ileus, due to vagal block, has been described. Paton (1951) suggested that it might be possible to produce ganglion-blocking agents more or less adapted to different ganglionic systems. It was with this purpose that Maxwell and Campbell (1953) investigated a large number of new drugs inhibiting synaptic transmission. Pentolinium was found active in lowering the blood pressure in smaller doses than hexamethonium, and it had only a weak action on gastric secretomotor activity. It is effective by mouth in a high proportion of cases, and it has been combined successfully in oral dosage with reserpine.

The research by Trapold *et al.* (1955) has been concerned mainly with the production of a ganglion-blocking agent consistently active by mouth. Ecolid has met this requirement and has also a longer duration of action than pentolinium. This increase in consistency and duration of oral action is accompanied by side-effects intermediate between those of hexamethonium and pentolinium. The treatment of our patients has been complicated by these side-effects. However, we have found that combined dosage of reserpine and ecolid by mouth affords a practical method for the treatment of hypertension, particularly in the smaller dosage required for the less severely ill patients, when side-effects are reduced.

Summary

A new hypotensive drug, ecolid, has been used in the treatment of severe hypertension. Consistent activity by mouth has been confirmed. The initial dose should not exceed 25 mg., and treatment consists of 25 to 200 mg. administered before breakfast, with a dose also during the evening, if required. It is more active than pentolinium, but side-effects are more severe ; the duration of action is longer. The combination of oral dosage of ecolid and reserpine has been found useful in the treatment of hypertension.

We are grateful to Dr. J. Gibson Graham, senior consulting physician, Royal Alexandra Infirmary, Paisley, for permission to record these observations, and to Ciba Laboratories Ltd., for supplying the drugs used.

References

Bain, C. W. C., Ashton, F., and Jones, B. P. (1955). *British Medical Journal*, **1**, 817.
Dale, H. H. (1914). *J. Pharmacol.*, **6**, 147.
Graham, J. G., and Maxwell, R. D. H. (1954). *British Medical Journal*, **2**, 1250.
Grimson, K. S., Tarazi, A. K., and Frazer, J. W. (1955). *Circulation*, **11**, 733.
Lyons, R. H., Moe, G. K., Neligh, R. B., Hoobler, S. W., Campbell, K. N., Berry, R. L., and Rennick, B. R. (1947). *Amer. J. med. Sci.*, **213**, 315.
Maxwell, R. D. H., and Campbell, A. J. M. (1953). *Lancet*, **1**, 455.
Organe, G., Paton, W. D. M., and Zaimis, E. J. (1949). Ibid., **1**, 21.
Paton, W. D. M. (1951). *British Medical Journal*, **1**, 773.
—— and Zaimis, E. J. (1949). *Brit. J. Pharmacol.*, **4**, 381.
Trapold, J. H., Plummer, A. J., and Schneider, J. A. (1955). *J. Pharmacol.* In press.

Medical Memoranda

Delayed Onset of Signs in Extradural Haemorrhage

Variations in the clinical picture resulting from extradural haemorrhage are common, but it is unusual for the development of signs of cerebral compression to be delayed for more than 24 hours after the receipt of injury. The compression, once initiated, is usually rapidly progressive, leading to death within 48 hours if unrelieved. In the following case, consciousness was never lost, the onset of clinical signs was insidious, and operation was not performed until six days after injury.

Case Report

On September 1, 1954, a boy aged 12 was riding downhill on his bicycle when the brakes failed. To stop the bicycle he put a foot between the spokes of the front wheel and was thrown over the handlebars, striking the right side of his head and his right leg on the ground. He did not lose consciousness, but vomited three times.

On admission to hospital he was found to be alert and bright, with good recollection of events before and after the accident. There were bruises in the right temporal region and over the right shin. The left eye had been removed in infancy following an injury, but the pupillary reactions on the right side were brisk and the optic fundus was normal. There was considerable haemorrhage from the right ear, and radiography showed a fine vertical fracture of the squamous part of the temporal bone on the right side. The pulse rate was 64.

Next day, apart from a little headache, the boy was well and the bleeding from the ear had stopped. Two days later

the headache had improved greatly and was only occasionally present. However, on September 6 he vomited once and said that his headache was worse. He was quite bright and spent most of the day reading. For the first time it was noticed that there was slight papilloedema on the right side.

A provisional diagnosis was made of subdural haematoma on the right side, and it was decided that an exploratory operation was necessary. This was carried out on September 7, a general anaesthetic being used in preference to local analgesia because of the patient's youth and the absence of any evidence of depressed conscious level. An anterior temporal burr-hole was made on the right side. This revealed an extradural clot, and so a temporal bone flap was raised in order to provide adequate access. A dark jelly-like clot 8 cm. in diameter and 2 cm. thick was found, extending down on to the base of the skull. When the clot had been removed there was haemorrhage from the anterior division of the middle meningeal artery, and this was stopped by diathermy. The bone flap was replaced and the scalp was sutured in two layers.

After the operation the patient made an excellent recovery and was discharged to his home on September 23.

Comment

It is possible that the bleeding from the ear provided decompression in the early stages. This may be the reason why no tentorial pressure cone was formed and no distortion of the perforating arteries occurred. If removal of the clot had been delayed it is probable that a blood cyst would have formed, as in the case reported by Rowbotham and Whalley (1952). Mental deterioration and more severe headache would then have resulted.

We wish to thank Dr. George Davison and Mr. G. F. Rowbotham for their help and for permission to publish this case report.

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References

Rowbotham, G. F., and Whalley, N. (1952). *J. Neurol. Neurosurg. Psychiat.*, 15, 64.

Case of Carcinoma of Third Part of Duodenum

Carcinoma of the duodenum is a rare condition which may be recognized radiologically. Its incidence is given as 0.3% of all gastro-intestinal carcinomata and 45% of small-gut tumours. The frequency of occurrence of the tumour at different sites of the duodenum is: 20% suprapapillary; 60% peripapillary; 20% infrapapillary.

Our case is thought to be of interest because it records a duodenal carcinoma occurring at its rarest site, a correct pre-operative diagnosis of the condition, and a tumour found to be resectable at laparotomy.

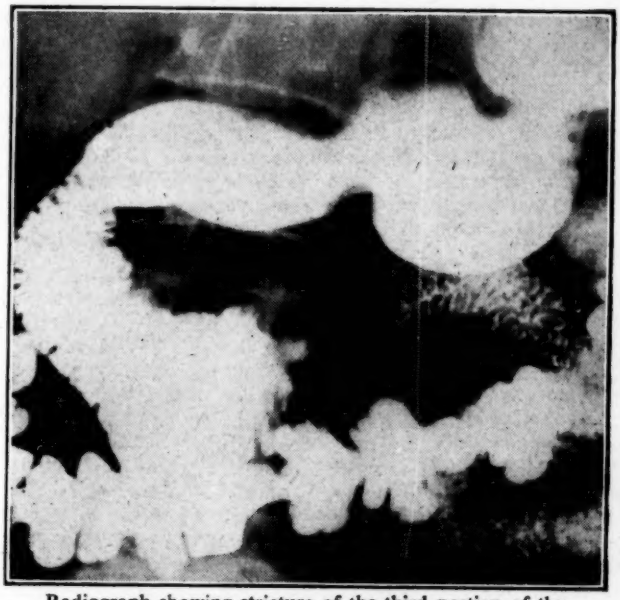
Dunhill (1952) and Rogers *et al.* (1952) reviewed the condition and described cases that had been under their care, as well as cases known to them. Freeman (1954) reviewed the literature on the subject, but could find only 24 cases of primary carcinoma of the infrapapillary portion of the duodenum diagnosed pre-operatively by radiology. In only 4 out of the 24 cases mentioned was the radiological diagnosis made with confidence; however, a post-operative scrutiny of the skiagrams of many proved cases indicated that a correct radiological diagnosis might have been made more often. In only 7 out of 24 cases seen at the Mayo Clinic was the diagnosis considered pre-operatively. Most cases are revealed at either laparotomy or necropsy. The age of the patients in whom the disease occurs is reported as varying from 44 to 64 years. Successful excision of the growth is uncommon; Eger (1933) states that only two cases known to him have lived longer than five years after operation. An increasing awareness of the existence of this tumour should stimulate a more careful radiological examination of the duodenum of patients with upper abdominal symptoms for which no lesion is found to provide a satisfactory explanation.

Most of the cases reported appear to have presented with palpable lumps, severe dehydration from prolonged vomiting, or, as in Dunhill's case, with symptoms arising from unsuccessful gastro-enterostomy. In cases suitable for operation the most desirable surgical treatment is resection of the growth and anastomosis of the divided gut. Either side-to-side or end-to-end anastomosis may be employed; and, judging by the results of operations performed in this manner, observers think that the dangers of denuding the posterior surface of the duodenum may have been exaggerated.

Case Report

A man aged 49 had had episodes of vomiting over a period of three months, but no previous indigestion. He frequently vomited bile-stained material. He had anorexia and had lost weight. Clinical features were indistinguishable from those of pyloric obstruction.

A barium meal showed stricture, with malignant features, of the third portion of the duodenum (see Fig.). No lesion of the oesophagus and stomach was revealed. Pathological report: R.B.C., 5,000,000; Hb, 76%; normal blood chemistry.



Radiograph showing stricture of the third portion of the duodenum.

At laparotomy the radiological diagnosis was confirmed. A tumour of the third portion of the duodenum, not fixed to the pancreas, was found, with moderate dilatation of the duodenum proximal to the tumour. There were no obvious secondary deposits in either the lymph nodes or the liver. The tumour, with a segment of gut extending from the second portion of the duodenum to include 6 cm. of the jejunum, was excised from beneath the mesenteric vessels. The jejunum was brought through the mesocolon to avoid the dissected area, and the ends of the divided gut were anastomosed. Catgut and linen thread were used for the through-and-through and sero-muscular sutures respectively. Histological report: adenocarcinoma.

Recovery was uninterrupted, and the patient was known to be alive and well six months after operation.

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References

Dunhill, Sir T. (1952). *Brit. J. Surg.*, 40, 13.
Eger, S. A. (1933). *Arch. Surg. (Chicago)*, 27, 1087.
Freeman, L. (1954). *Brit. J. Radiol.*, 27, 301.
Rogers, K. E., Goligher, J. C., and Williams, E. R. (1952). *Brit. J. Surg.*, 40, 1.

Reviews

A NEW TRANSLATION OF FREUD

The Interpretation of Dreams. By Sigmund Freud. Translated from the German and edited by James Strachey. (Pp. 662+xxxii. 21s.) London: George Allen and Unwin Ltd. 1955.

There have been two previous English translations of this famous book, both very unsatisfactory. The present one is an entirely new translation by the leading English translator of psycho-analytical works, whose impeccable English, familiarity with the subject-matter, and colloquial knowledge of German are all beyond reproach. No longer are other people's dreams substituted for Freud's own, since Mr. Strachey has patiently explained the plays on words that daunted the previous translator.

But we have here much more than a simple translation—namely, a true variorum edition, for Mr. Strachey has edited as well as translated the original. For the first time we can perceive easily and clearly the various changes Freud introduced in the eight German editions, omissions as well as additions, and often the reasons for these changes are given. Then the whole work has been enriched by a number of explanatory footnotes which make any obscure allusions more comprehensible. There are two appendices, one being a list of other writings by Freud dealing with the topic of dreams. There are two full bibliographies—one of the works referred to in the text, the other being a list of works on the subject previous to the publication of the present one. There is a complete list of the dreams mentioned in the text, Freud's own and dreams by others being separately listed. In a lengthy introduction Mr. Strachey describes both the history of the book itself and that of the development of Freud's ideas on the subject. There is an unusually full and well-grouped index. It will be seen, therefore, that we have here a classic model of how an important scientific work should be presented, one of which the editor, his assistants, and publisher may all be proud.

The volume is a worthy presentation of Freud's magnum opus. As is well known, Freud's fame rests very largely on this single work. It was his most original contribution to psychology, the one of which he himself thought most highly. The theme itself, the method of interpreting dreams, was of the utmost value to him personally. Whenever in doubt about his other findings or conclusions it was always *The Interpretation of Dreams* to which he referred as his sheet anchor. We are concerned here with the present volume rather than with the scientific content and value of the original work, but it is gratifying to know how much more accessible this volume will make it.

Finally, the remarkably low price of such a book is noteworthy.

ERNEST JONES.

REPRODUCTIVE ENDOCRINOLOGY

Hormones in Reproduction. British Medical Bulletin, Volume 11, No. 2. (Pp. 83–170. 15s.) London: British Council. 1955.

It is appropriate that the May, 1955, number of the *British Medical Bulletin* should be devoted to reproductive endocrinology, for it was exactly 50 years previously that F. H. A. Marshall and W. A. Jolly read before the Royal Society of London a paper on the ovary as an organ of internal secretion. Under the capable guidance of Dr. A. S. Parkes, who has acted as scientific editor as well as writing a paper on the endocrinology of the testis, 18 contributors of international standing in the field of reproductive endocrinology have combined to present 16 articles on aspects in which they are specially interested. The result is an exposition of current knowledge and theories, well referenced and authoritative, but naturally not, in a volume of this size, comprehensive, even though the contributors range from A (Amoroso) to Z (Zuckerman). The doctor who picks up this book, initially probably to read Dr. Eleanor Venning's assessment of the clinical value of hormone assays or Dr. G. I. M. Swyer's discussion of the hormones in relation to human fertility, will almost certainly read on, to his instruction and enjoyment, the papers on physiological, biochemical, and biological aspects; not surprisingly, for the hormones of reproduction make bedfellows of us all.

S. BENDER.

ESSAYS ON ANAESTHESIA

Mysterious Waters to Guard. Essays and Addresses on Anaesthesia. By Wesley Bourne, M.D., F.F.A.R.C.S. (Pp. 398; illustrated. 42s.) Oxford: Blackwell Scientific Publications. 1955.

The intriguing title of this collection of essays and addresses on anaesthesia refers to the living cell, which, as the author in his inimitable style says, must be "guarded, so perhaps to influence their ripple or even surging sea, not only in health but also when drugs that are given inevitably ruffle the harmony." The author was a great pioneer in that borderland between pharmacology and practical anaesthesia, and it is a pleasure to read once again papers which in their day represented the spearhead of the New Anaesthesia. Wesley Bourne is known for his philosophic and somewhat mystical outlook on anaesthesia as well as for his classical erudition. These essays do not make easy reading, for they are written in what would now be regarded as an exceptionally elegant style, more than liberally sprinkled with quotations from the classics of the world. Indeed, the author does not hesitate to quote from the Latin, Greek, and even the Russian, though as a gesture to the less knowledgeable reader he translates the latter.

The steady advance of anaesthesia from the simple ether-dropping stage to the complex scientific affair it is to-day is seen in retrospect as Wesley Bourne's essays are read. As biochemical and physiological studies extended, new meanings became attached to phrases like "sufficient oxygen" and "adequate airway." Here and there ideas are propounded which were new in their day but have now been discarded. Such, for example, is Bourne's advocacy, as recently as 1942, of spinal anaesthesia with the retention of the cough reflex for thoracic operations on tuberculous patients.

Included among these essays is an account of a visit to Britain just after the war. The warm humanity of Wesley Bourne peeps from every line as he recounts his reactions to his social contacts in this country. Scattered through the book are a series of portraits of men in various fields of medicine, each of whom should be glad to be counted among Wesley Bourne's friends. Those of British anaesthetists form a good cross-section of the leaders of the last generation, though more up-to-date photographs of some of them would have been more easily recognized by present-day anaesthetists.

This volume is a worthy addition to the more elegant literature on anaesthesia, and will be particularly valued by anyone who has had the good fortune to come in contact with Wesley Bourne and to feel the warmth of his lovable personality.

W. W. MUSHIN.

INTESTINAL SURGERY

Surgery of the Small and Large Intestine. By Charles W. Mayo, M.D. Illustrated by Russell Drake. (Pp. 340; illustrated. 68s.) Chicago: Year Book Publishers Inc. London: Interscience Publishers, Ltd. 1955.

The series of handbooks on operative surgery produced by the Year Book Publishers are already quite well known. The present volume, entitled *Surgery of the Small and Large Intestine,* is really complementary to a previous one on the

stomach and duodenum, and as the general format is similar in both they together constitute a two-volume treatise on the alimentary canal.

Dr. Charles Mayo (famous son of a famous father) has written the text to some 94 plates of excellent clear line drawings by Mr. Russell Drake, head of the art studios of the Mayo Clinic, a pioneer department which from its inception has always been renowned for its superb medical illustrations. The book might indeed have been called an atlas, for the drawings are its main feature, to which the text forms, except in some pages of general matter, a commentary. Random selection of certain subjects to test the teaching of the book reveals it to be sound, sensible, and up-to-date. Thus, under the heading "Regional Enteritis" it is advised that medical therapy should be the normal treatment and surgery resorted to only when complications are present; while, in view of the added risk of fistula formation, it is commanded that the appendix "be not removed in the presence of enteritis unless the disease is definitely confined to the region above the ileocaecal valve." This statement is so dogmatic that it is a pity the ambiguous term "above" should have crept into it. To another of the test subjects, however—namely, argentaffin tumours—no reference could be found.

The difference between illustration and performance in surgery is great, perhaps greater than in any other subject. Nevertheless for teaching purposes there can be no doubt that the idealized operation of the drawing-board has many advantages, and as such there can be no criticism of Mr. Drake's work.

This is a straightforward work which contains all that the student and junior surgeon require to know of the technique of intestinal surgery; the abundant illustrations visualize many points which could only be described, and then far less clearly, by much letterpress.

NORMAN C. LAKE.

THE DIENCEPHALON

Diencephalon: Autonomic and Extrapyramidal Functions. By Walter Rudolph Hess, M.D. (Pp. 79+xii; illustrated. 25s.) London: William Heinemann Medical Books Ltd. 1954.

Professor Hess's life-study of the physiology of the brain stem has constituted one of the important milestones in our advancing knowledge. All his publications have, however, appeared in German, and there has not so far been a single detailed review of his work in the English literature, apart from a recent valuable abstract by P. Gloor in the *Archives of Neurology and Psychiatry* (1954, **71**, 773).

Professor Hess has now himself condensed an account of his methods, his results, and their implications into a very short monograph, which contains a detailed bibliography of his publications as well as that of some workers in similar fields. It is most surprising that after retirement Professor Hess should have been able to condense his monumental work—which needs eight pages for its bibliography—into sixty short and profusely illustrated pages. It is a measure of the importance of his work that he has been able to do so, and the English-speaking neurologist, whether working in the laboratory or the ward, is indebted to him.

DENIS WILLIAMS.

SURGICAL PATHOLOGY

Pathology for the Surgeon. By William Boyd, M.D., F.R.C.S.(Canada), F.R.S.(Canada), F.R.C.P.(London), LL.D., D.Sc. Seventh edition. (Pp. 737+vi; illustrated. 87s. 6d.) Philadelphia and London: W. B. Saunders Company. 1955.

The fact that this textbook has in thirty years reached its seventh edition is sufficient evidence of its practical value and of the high position held in the world of pathology by its distinguished author, Professor Boyd. His wide experience enables him to express with clarity subjects which are often obscure, and to assess the value of the various and often conflicting views which may be held. Beautifully illustrated with typical examples, the whole volume is a masterpiece of careful selection, close reasoning, and admirable presentation. For the student it is a gold-mine; for the surgeon it will be an inspiration, and often a warning.

Under the general pathology of tumours a full discussion is given of modern views of the origin and spread of cancer; and the application of these later on to the special case of cancer of the breast will give many surgeons cause for thought. There could be no better example of the importance of a thorough knowledge of pathology and of the effect which it may have upon vital surgical decisions. From such complex and perplexing considerations it is a pleasure to turn to a superb article on the gall-bladder, and to feel that here at any rate we are sure of our foundations in surgical practice.

HENRY SOUTTAR.

PSYCHIATRIC TREATMENT

Treatment in Psychiatry. By Oskar Diethelm, M.D. 3rd edition. (Pp. 545+xii. 69s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1955.

The day is past when an author, however accomplished, can compress a satisfactory account of all forms of psychiatric treatment into one volume. Professor Diethelm's book, first published 20 years ago, outlines a large number of psychotherapeutic measures and also treatment by physical and chemical agents and by surgery. Adolf Meyer's distributive analysis and synthesis is the basis for the method, designated "dynamic psychotherapy," which appeals to the author. This "goal determined" treatment is described as "an analysis along selected dynamic lines and life situations." From the description it will be seen that the treatment is mainly on a conscious level.

A separate chapter is devoted to Freud's *Psycho-analysis*, and for good measure there is a further chapter on other psychotherapeutic procedures, but this is so condensed as to be seriously misleading—for instance, the strange statement that Jung's *Analytical Psychology* is "in many ways a synthesis of Freud and Adler but developed along independent lines." Hypnosis and suggestion, which may sometimes be used in "distributive analysis," are discussed in one of the best chapters of the book. The author is, however, incorrect in his statement that hypnosis was first worked out scientifically by Bernheim and Liébeault. The credit belongs to James Braid, who coined the word "hypnosis," and his brilliant description of it has never been surpassed. Braid's observations on the nature of hypnosis were in fact adopted and extended by the French workers.

The sections on electric convulsion therapy, insulin shock therapy, and the administration of drugs provide an excellent introduction to the subject. The treatment of alcoholism, sexual difficulties, stuttering, and compensation reactions follow conventional lines and are practical and well presented, although too much space is given to description and not enough to treatment. Many authorities are quoted in the book, but their names are not mentioned in the index, nor is there an index of authors. This is unfortunate in a volume which has much to commend it as a book of reference.

E. A. BENNET.

Mr. J. Lyle Cameron's booklet, *Motherhood and the Safe Time Simplified*, will be very useful for doctors to hand to those patients who on medical grounds are advised to avoid pregnancy and who on religious grounds object to artificial means of contraception. Couched in the simplest terms, it explains the safe-period method in a manner that anyone with ordinary intelligence could understand, at the same time pointing out its difficulties in cases where the menstrual periods are not regular. The booklet, which is published by E. and S. Livingstone, Ltd., price 9d., will be equally useful in reverse for aiding cases of relative sterility.

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CORTISONE

Cortisone and hydrocortisone will be generally available throughout the country on prescription from December 5, and it may be helpful, therefore, briefly to review the use of these and allied steroids in everyday clinical practice. The remarkable therapeutic properties of cortisone were first announced six years ago, and since then a gradually increasing use of steroids in Britain has familiarized first research workers, then selected hospitals, and finally all hospital staff with the advantages and disadvantages of these powerful substances. Cortisone is now manufactured in this country, and the cost has decreased, but it is still a very expensive drug. An unprecedented output of "literature" has documented our rapidly advancing knowledge of the chemistry, physiology, and metabolism of these substances and of their action in health and disease, but there is still much controversy, especially about practical aspects of therapy. Even here, however, a measure of agreement has been reached, though there will always be the perennial enthusiast and the perpetual cynic to greet each new analogue as it arrives.

Before all else it is important to realize that cortisone is not a cure for any disease, except, perhaps, when used for replacement in Addison's disease or hypopituitarism. When given to patients with intact or abnormally active adrenal glands it suppresses production of corticotrophin by the pituitary and consequently the release of endogenous hydrocortisone by the adrenal gland. This suppression lasts only as long as the cortisone is given. In diseases other than adrenal insufficiency it acts by suppressing some of the "host-components" of disease, as seen in hypersensitivity and the inflammatory response. Again its effects last for as long as it is given, but the adrenal gland takes a few days to get over its inhibition, and special care must be taken to taper the dosage gradually so as to allow endogenous production of hydrocortisone to be resumed before administration of the drug is finally stopped. Unless this is done the underlying disease, if still even slightly active, will flare up violently again.

The fields of clinical practice in which these substances are most useful are the rheumatic diseases, including "collagenoses," diseases of the skin and of the eye, certain blood diseases, and allergy. In rheumatic fever cortisone has been shown to be beneficial and about equal to aspirin in its overall effect. This is the conclusion of a large controlled trial[1] in which most of the centres interested in rheumatic fever in Great Britain and North America participated. Others have claimed that a higher dosage than that given during the trial, either of salicylate[2] or of cortisone—or a combination of both drugs[3]—leads to better results, but the claims for high cortisone dosage are not accompanied by adequate evidence,[4] and all need confirmation. In rheumatoid arthritis again, despite the dramatic immediate improvement, two long-term controlled trials against aspirin,[5 6] in which a fairly safe mean maintenance dosage of 75 mg. of cortisone per day was given, have shown no consistent clinical difference between the two treatments after six, twelve, or, in the earlier trial, after 24 months.[7] Some patients undoubtedly respond better to cortisone than to salicylate or phenylbutazone, but a therapeutic trial is needed to identify these. It must be remembered that cortisone or salicylate medication is only one aspect of routine care which includes, among other measures, splintage and physiotherapy.

Of the collagen diseases, scleroderma is usually resistant to hormone therapy, while periarteritis nodosa and lupus erythematosus are responsive to it; life is prolonged for a period and rendered less unpleasant, although there is probably little effect on the progress of established renal disease or on the ultimate outcome. Very high dosage may sometimes be needed, and a daily supplement of potassium chloride (3 g.) must be given to make good the increased potassium excretion by the kidney. Other diseases often temporarily suppressed by cortisone include iritis and interstitial keratitis, exfoliative dermatitis,

[1] Joint Report by the Medical Research Council of Great Britain and the American Heart Association, *British Medical Journal*, 1955, **1**, 555.
[2] Illingworth, R. S., Doxiadis, S. A., Lorber, J., Philpott, M. G., and Stone, D. G. H., *Quart. J. Med.*, 1954, **23**, 177.
[3] Holt, K. S., Illingworth, R. S., Lorber, J., and Rendle-Short, J., *Lancet*, 1954, **2**, 1144.
[4] Heffer, E. T., Turin, R. D., Slater, S. R., and Kroop, H. G., *J. Pediat.*, 1954, **44**, 630.
[5] Report by Joint Committee of the Medical Research Council and Nuffield Foundation, *British Medical Journal*, 1954, **1**, 1223.
[6] Report of Merck Trial Subcommittee of Empire Rheumatism Council, *Ann. rheum. Dis.*, 1955, **14**, 212.
[7] Empire Rheumatism Council's Multi-centre Controlled Trial Comparing Cortisone and Aspirin in the Long-term Treatment of Rheumatoid Arthritis: Results up to One Year, *Ann. rheum. Dis.*, 1955, **14**, in the press.
[8] Symposium in the *Practitioner*, November, 1955.
[9] *Cortisone and A.C.T.H. in Clinical Practice.* Edited by W. S. C. Copeman, 1953, London.

pemphigus, drug sensitivities, Stevens–Johnson syndrome, thrombocytopenic purpura, acquired haemolytic anaemia, sarcoidosis, and status asthmaticus not responding to adrenaline and aminophylline. In this last condition a high initial dosage may be necessary and hydrocortisone (free alcohol) be given in an intravenous glucose-saline drip. In chronic asthma and leukaemia the results of cortisone treatment have been disappointing. When doses of over 50 mg. per day are continued for any length of time, potassium chloride supplements and a low-salt diet are desirable.

Before embarking on cortisone therapy, the physician might well ask himself three questions. First, is the disease likely to react better to cortisone than to another potentially less dangerous drug? This implies that the diagnosis is known: cortisone should never be given at random. Secondly, has the patient any condition such as latent tuberculosis, cardiac failure, hypertension, or gastric ulcer which might give rise to dangerous or fatal reactions? Before this question can be answered *x*-ray examination of the chest may be necessary. Thirdly, is treatment with cortisone to be a temporary or a semi-permanent measure, and, if the former, when and how is the administration of the drug to be stopped? The longer the treatment and the higher the dosage, the greater is the frequency of serious complications. These make a formidable list, and include psychoses; perforation or bleeding within the gut; silent fulminating infections such as appendicitis; pneumonia or miliary tuberculosis; hypertension; phlebothrombosis; and osteoporosis leading to vertebral collapse. Other side effects such as obesity, hirsutism, and glycosuria are temporary and of little account, although retention of water and salt may be serious in patients with latent heart failure. The new analogue, prednisone, released as yet only to hospitals, is better used when there is a danger of heart failure, since it has less salt-retaining effects. Some of these "side effects" such as psychosis or hypertension necessitate discontinuation of therapy; others, reduction of dosage—perhaps to a level where therapeutic benefit is not apparent. Infections should be promptly detected and treated, but it is wise not to reduce hormone dosage until antibiotic therapy has taken effect, and then, as always, to reduce the dose gradually.

Powerful drugs such as cortisone increase the physician's responsibility and his power, not only to do good, but, by inadvertence, harm also, and when considering their use he would do well to turn to the original sources in the medical journals or guides prepared for the purpose: it is hoped soon to publish such a one in the *Journal*. Such guides[8 9] are based largely on hospital practice, with specialist experience and ready facilities for biochemical and bacteriological tests. It is only by a wider and more general use and appraisal that the practical everyday value of these new substances will emerge.

PROTECTION OF INFANTS AGAINST TUBERCULOSIS

It has been estimated by R. M. Cammock and F. W. J. Miller[1] that at least 5% and possibly as many as 10% of infants infected with tuberculosis under 2 years of age develop serious complications within two years of infection. The morbidity from tuberculous meningitis and miliary tuberculosis is highest in the first three years of life. In recent years the incidence of tuberculous infection in infants has fallen as a result of higher standards of living, increasing alertness of the preventive services, the widespread use of B.C.G. for contacts, and the more efficient treatment of sputum-positive cases. The prognosis for children with progressive types of tuberculosis has greatly improved with the introduction of new drugs and with increasing experience in their use. Nevertheless there are still many infants who become infected in the first years of life, and some of them die as a result of that infection. B. Briggs, R. S. Illingworth, and J. Lorber[2] were able to trace a human source of infection in 155 out of 174 (88%) tuberculous infants under 2 years of age. Most of the contacts lived within the same household. This is a strong indication that more could and should be done to prevent tuberculosis in infants. The problem resolves itself into two parts—the prevention of tuberculous infection and the prevention of tuberculous disease in those already infected. In his Leonard Parsons Memorial Lectures, published in this and last week's issues of the *Journal*, Professor Wilfrid Gaisford outlines the most important measures to prevent infection in infants. Among these are separation of the infant from anyone in the household with tuberculosis until it is safe to resume contact after a successful B.C.G. vaccination; routine radiography of pregnant women to discover sources of infection at the earliest moment; the provision of special maternity units for the

[1] Cammock R. M. and Miller F. W. J., *Lancet*, 1953, **1**, 158.
[2] Briggs, B., Illingworth, R. S., and Lorber, J., ibid., 1955, **1**, 263.
[3] Lorber, J., *British Medical Journal*, 1953, **2**, 1122.
[4] —— *J. roy. Sanit. Inst.*, 1954, **74**, 99.
[8] Wallgren, A., *Acta Paediat. (Uppsala)*, 1955, **44**, 237.
[9] *British Medical Journal*, 1955, **2**, 1072.

delivery of tuberculous women; and the raising of standards of hygiene, including better education, of tuberculous persons. This last point cannot be stressed enough: tuberculous adults far too often appear to be unaware that they may be dangerous to children who have not been protected by B.C.G. vaccination. All children who may come into regular contact with them should be given B.C.G., irrespective of whether they live in the same house or not.

The safety and efficiency of B.C.G. vaccination are now well recognized. Professor Gaisford found that vaccination at birth is fully effective, though naturally this does not obviate the need for segregation. Nearly 1,000 infants and young children who were contacts of cases of tuberculosis were vaccinated by him in Manchester, and none died of tuberculosis and none developed a recognizable tuberculous lesion in four years. Lorber[3] made similar observations on infants from tuberculous homes who were vaccinated in Sheffield. Whether revaccination of these children will be necessary in later years is not yet known, but the immediate saving of life is considerable. The dosage, the type of vaccine to be used, and the question whether vaccination should be extended to all newborn infants or should be reserved for potential contacts (taken in the broadest sense of the word), as is done at present, are problems to which final answers cannot be given. Professor Gaisford's experiments in successively reducing the dose of Wells's vole bacillus vaccine and of mixing live and dead bacilli without significant reduction in the conversion rate suggest that it may become possible to use this vaccine without the now common complication of axillary lymphadenitis. Another new development is the use of freeze-dried B.C.G. vaccine, at present under trial. This may have advantages, especially if mass vaccination of newborn infants is considered, for it produces only small local lesions. There is commonly a delay in the appearance of tuberculin allergy after freeze-dried vaccines have been given, but in non-contacts this would not be a disadvantage.

Mass vaccinations of all infants would be a vast administrative undertaking, and the additional effort and money that would be necessary for that purpose could perhaps be used to better advantage in the earlier diagnosis of infectious tuberculosis and the eradication of the sources of infection.[4] As Professor Gaisford suggests, it might not be difficult to introduce B.C.G. vaccination of all newborn infants in those maternity hospitals where there is already experienced paediatric supervision. In the Scandinavian countries mass vaccination of the newborn is commonly practised, but even Professor A. Wallgren[5] now believes that this practice in countries with a relatively low tuberculosis mortality is no longer essential. What matters is the careful but urgent selection of all those infants for B.C.G. vaccination who are at all likely to come into contact with tuberculosis. As Wallgren says, it would be neglect not to vaccinate such children.

A fortnight ago we discussed in these columns the pros and cons of giving isoniazid and other drugs to prevent tuberculous illness in infants who have recently been infected but who have no symptoms of illness.[6] Only controlled trials can answer the question whether such treatment reduces the risks of infection. Meanwhile the careful supervision of infected infants, whether treated with antibiotics or not, should prevent death, and the early recognition and efficient treatment of haematogenous complications will lead to complete recovery in almost all cases.

THE RUSSIAN DOCTORS

The dinner held in the Great Hall of B.M.A. House last Friday was the final ceremony attended by the six Russian doctors who have been the guests of the Association during the past three weeks. In proposing the health of the guests the Chairman of Council, Dr. E. A. Gregg, expressed the thanks of the Association to the many organizations and individuals who had helped to entertain the Russian visitors, and in particular the Soviet Relations Committee of the British Council. The willing help that came from those who in England and Scotland showed our guests the various aspects of medical life and activity in Britain convinced them, we may be sure, that the desire for exchange of knowledge and experience is very real, as, too, is the desire for friendship with professional colleagues pursuing the same ends. All who came into contact with the Russian delegation were impressed by their eagerness to learn of progress in British medicine, and by the unaffected friendliness they so quickly established with those they met on formal and informal occasions. Dr. Gregg underlined this when he said: "There is a brotherhood of medicine which recognizes no frontiers, and we are delighted that our Soviet colleagues have come on this occasion at the invitation of their professional brothers, represented by the British Medical Association." The Minister of Health, Mr. Iain Macleod, voiced his approval of this when he subsequently said that the Government had encouraged the British

Council to set up a Soviet Relations Committee to stimulate exchanges between the two countries. That the recent visit has been a successful move in this direction was made clear in the speech made at last week's dinner by the leader of the Russian delegation, Professor S. A. Sarkisov. Accounts of the dinner and of the visit appear elsewhere in this issue. It is to be hoped that they record the beginning of a new and freer exchange of ideas and knowledge between the medical men and women of Britain and the U.S.S.R. to the continuing benefit of both.

SCHOOLCHILDREN'S WARTS

Many dermatologists in Britain and the United States believe that the incidence of warts has increased in recent years. Satisfactory proof that they have is difficult to obtain, but there can be no doubt that warts cause their victims no little embarrassment and discomfort and that their treatment puts an unwelcome burden on general practitioners, school medical officers, and dermatologists. The infective origin of warts has been generally accepted since Jadassohn's successful inoculation experiments in 1896. Although it is still widely believed that warts of different clinical forms are produced by the same virus, the researches of M. J. Strauss and his colleagues[1] and of A. Lyell and J. A. R. Miles[2] suggest that there may be two types of wart, possibly caused by different viruses.

Most epidemiological studies have been based on the selected cases referred to hospital or school clinics. The investigation recently carried out by the East Anglian Branch of the Society of Medical Officers of Health[3] is therefore of particular interest in that 13,423 schoolchildren in 107 schools were examined. Plantar warts were present in 0.65% and other warts in 9.71%. The incidence of warts of both types increased with age in both sexes. Plantar warts, but not other warts, were twice as common in girls as in boys. In each school there was a direct relationship between the incidence of plantar warts and of other warts. The greater frequency of plantar warts in girls has often been reported, and it has been suggested that such feminine activities as dancing or physical training in bare feet may provide special opportunities for the transmission of the infection. Such explanations are not entirely convincing; it is possible that girls are inherently more susceptible than boys and that if the incidence is higher in barefoot dancers it is because most barefoot dancers are girls. The importance of swimming-baths, gymnasiums, and changing-rooms in the spread of plantar warts is unknown and is difficult to investigate, since activities out of school hours may invalidate conclusions based on the presence or absence of certain recreational facilities provided by the authorities. The constant relationship between the incidence of plantar warts and other warts in East Anglia and the lack of significant local differences in the incidence of plantar warts throughout the region suggest that direct transmission of the infection from foot to foot is certainly not the only way in which plantar warts are contracted, important though it may be. The incubation period of warts after experimental inoculation ranges from one to twenty-one months,[4] and this variability increases the difficulties of epidemiological studies. Further large-scale statistically controlled investigations are required before prophylactic measures can be effectively planned.

However warts are transmitted, the advantages of early treatment cannot be disputed. In some districts warts are efficiently treated with carbon-dioxide snow at school clinics. This is a sensible arrangement which avoids unnecessary delay, and it reduces the absence from school which attendance at hospital may require.

[1] Strauss, M. J., Bunting, H., and Melnick, J. L., *J. invest. Derm.*, 1950, **15**, 433.
[2] Lyell, A., and Miles, J. A. R., *British Medical Journal*, 1950, **2**, 1119.
[3] *Med. Offr*, 1955, **94**, 55.
[4] Rulison, R. H., *Arch. Derm. Syph. (Chicago)*, 1942, **46**, 66.

NEW RESPIRATORY VIRUSES

The U.S. public health service announced last week that a new vaccine has given "substantial protection" against the adenoidal–pharyngeal–conjunctival (A.P.C.) viruses.[5] These seem to play some part in causing certain types of acute febrile upper respiratory catarrh,[6 7] and the prototype of one group is the RI-67 agent of M. R. Hilleman and J. H. Werner.[8]

During the last war the U.S.A. Commission on Acute Respiratory Diseases conducted three extensive experiments on human beings in an attempt to define the causal agent of primary atypical pneumonia.[8 9] In the first experiment, in October, 1943, untreated throat washings and sputa were sprayed into the respiratory tracts of twelve male volunteers in a civilian camp at Gatlinburg, Tennessee. Within 7 to 22 days of the inoculation ten recipients developed respiratory tract infections of varying severity; three showed minimal changes in chest radiographs. Encouraged by these results, the Commission conducted further transmission experiments in the summer of 1944 in North Carolina. Throat washings and sputa were collected from what were considered to be characteristic cases of primary atypical pneumonia. This material was pooled and divided into three parts—untreated, Seitz-filtered, and autoclaved—and sprayed into the respiratory tracts of three different groups of volunteers. Whereas the recipients of the autoclaved material remained well, those receiving both unfiltered and filtered inocula developed mild upper respiratory tract infections or pneumonia. It is probable that many respiratory tract viruses were transmitted, so contributing to the

[5] *The Times*, November 4, 1955.
[6] Zaiman, E., Balducci, D., and Tyrrell, D. A. J., *Lancet*, 1955, **2**, 595.
[7] Huebner, R. J., Rowe, W. P., Ward, T. G., Parrott, R. H., and Bell, J. A., *New Engl. J. Med.*, 1954, **251**, 1077.
[8] Commission on Acute Respiratory Diseases, *J. clin. Invest.*, 1945, **24**, 175.
[9] Commission on Acute Respiratory Diseases, *Johns Hopk. Hosp. Bull.*, 1946, **79**, 97 and 109.
[10] Rowe, W. P., Huebner, R. J., Gilmore, L. K., Parrott, R. H., and Ward, T. G., *Proc. Soc. exp. Biol. (N.Y.)*, 1953, **84**, 570.
[11] Hilleman, M. R., and Werner, J. H., ibid., 1954, **85**, 183.
[12] Ginsberg, H. S., Badger, G. F., Dingle, J. H., Jordan, Jr., W. S., and Katz, S., *J. clin. Invest.*, 1955, **34**, 820.

confusion in the clinical pattern of the resulting infection. Other factors influencing the severity of the infection included the virulence of the agents, the susceptibility of the patient and his respiratory defence mechanism, and the presence of associated bacteria.[9] At the time no causal agent was identified, and interest in these decade-old experiments would have been historical only but for the recent discovery in the U.S.A.[10 11] of the new group of viruses. The Commission then re-examined sera stored from the original transmission experiments, and with illuminating results.[12] Some specimens of sera taken at the acute stage of the illness and again during convalescence from the original donors and from the volunteer recipients had been kept lyophilized at room temperature or stored in liquid form at 4° C. Significant titres of neutralizing antibodies to the RI-67 agent indicated specific infection with these new respiratory viruses. The cause of at least one of the respiratory infections transmitted in 1944 seems to be established. It is fortunate that the Commission, and Dr. John H. Dingle in particular, had the foresight to store these sera for so long. Had our heritage from the world influenza pandemic of 1918 been so bountiful, our doubts about its aetiology would have been largely resolved. It is a lesson to be remembered for any mysterious epidemics, such as that running its course at the Royal Free Hospital. Although results are retrospective they can but add to the sum of our knowledge of infectious diseases.

NEW ANTIBIOTIC FROM THE U.S.S.R.

A paper by one of the six distinguished Soviet medical scientists who have recently visited this country appears at page 1177 of the *Journal* this week. Professor G. F. Gause may be remembered as the author of another paper[1] in English nine years ago on the properties of an earlier antibiotic, "gramicidin S." Albomycin, which he describes now, seems to be a discovery of much greater importance; indeed, several of its properties are unique. It is a peptide containing one unidentified and six identified amino-acids, and 4.16% of iron. The presence of this metal, and the fact that the activity of albomycin is entirely lost under anaerobic conditions, have led to the suggestion that it may interfere with the action of an enzyme that contains iron and transports oxygen. Presumably an effect on respiration has been demonstrated by the usual Warburg method. It inhibits the growth of staphylococci in an extreme dilution (1 in 7×10^8), which credits it, in these terms, with an activity about ten times greater than that of penicillin. Other sensitive organisms include not only the other pyogenic cocci, with the unusual exception of some strains of haemolytic streptococci, but several intestinal Gram-negative bacilli, including dysentery bacilli. If activity against these is of the same order, albomycin combines "broad spectrum" qualities with efficacy in extreme dilution seen hitherto only in penicillin and to a less extent in erythromycin, and mainly confined in them to Gram-positive species. It is unexpected that *Bacillus mycoides* should be resistant, while a closely related species, *B. subtilis*, is sensitive. It is not surprising, in view of this unusual range of activity, that there should be no cross-resistance between albomycin and other antibiotics.

In the information given about the behaviour of albomycin in the body quantities are expressed in units. There is something to be said for this, since the unit is the minimum amount per ml. which will inhibit the growth of staphylococci, and units in the plural are thus multiples of the minimum effective concentration. On the other hand, a statement already quoted about the action of albomycin on staphylococci shows the unit to be a minute amount in terms of weight, approximately 0.0014 μg. Thus the apparently enormous dose of 50,000,000 units per kg. which proved non-toxic to mice means only 1.4 mg. to a 20 g. mouse. Pharmacological study has revealed a most valuable property—namely, that albomycin persists in the blood in effective concentrations after a single subcutaneous dose for as long as two or three days. There appears to be some discrepancy in the account given of the rate of excretion, since it is said in the text that 70–80% of the injected dose is excreted in the urine within six to eight hours, whereas the graph of blood concentration shows a fall of only between 40% and 50% in this time. The recorded levels are remarkably high, and even seem to indicate a selective concentration in the blood, since the dose given, if uniformly distributed in the body, would produce 100 units per ml. in the blood, and the level is shown to remain higher than this for about 24 hours. This long persistence is attributed to combination with and slow release from plasma proteins. There is nothing unusual in this, since penicillin and chlortetracycline have both been shown to form such combinations, though on penicillin particularly this reaction confers no such lasting effect. What is unusual, apart from the slow dissociation of the albomycin-protein combination, is that concentrations up to 150 units (0.21 μg.) per ml. are wholly combined while amounts in excess of this remain free, and that the combined antibiotic can be freed for titration by the drastic procedure of trichloracetic-acid protein precipitation.

Animal experiments have shown that albomycin is therapeutically active, and this activity has been confirmed clinically, mainly in coccal infections. Nothing could better illustrate the difference in experience with antibiotics in the U.S.S.R. from that in the English-speaking world than the mention of infections due to penicillin-resistant pneumococci and gonococci. These are organisms which we never see, and more information about the circumstances of their appearance, prevalence, and degree of resistance would be of the greatest interest. We should moreover like to know much more about albomycin and have an opportunity of studying it ourselves. In the *rapprochement* which now seems to be in progress it would be a graceful gesture on the part of the U.S.S.R. to make such study possible. Either a quantity of albomycin might be made available to at least a few leading research centres in other countries, or its actual production elsewhere might be permitted under appropriate conditions.

[1] Gause, G. F., *Lancet*, 1946, **2**, 46.

EMERGENCIES IN GENERAL PRACTICE

APOPLEXY

BY

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For the purposes of this article apoplexy may be defined as a malady of sudden onset characterized by depression of consciousness and evidence of severe local damage to the brain.

The clinical picture thus defined is one that is familiar to all in general practice and is probably one of the commonest medical emergencies to which general practitioners are called. Sometimes the patient will be dead on the doctor's arrival, more often death will take place within a few hours and before the patient can be moved to hospital or a second opinion obtained, should either of these steps otherwise have been deemed desirable. In other cases the victim survives the immediate effects of the ictus and the doctor will be faced with decisions concerning management, treatment, and prognosis. These are problems of considerable difficulty, and they become more so as each decade adds its quota of advances in medicine and surgery. Before they can be solved in a rational manner it is essential that an accurate diagnosis should be made, and this diagnosis, in the first place, has to be made by the only person in a position to make it—the general practitioner.

There are two distinct stages in the diagnosis of apoplexy—namely, to distinguish apoplexy from other conditions causing loss of consciousness and then to determine which of the possible causes of apoplexy is responsible for the particular case.

Recognition of Apoplexy

Apoplexy very rarely causes sudden death in the sense that coronary thrombosis or rupture of the heart does. Even though consciousness is lost instantaneously it is almost unknown even for the most disastrous cerebral vascular accident to kill in less than five or ten minutes. Apoplexy, however, is a not uncommon cause of a patient being found dead in circumstances in which the mode of dying is unknown.

The principal group of conditions from which apoplexy has to be differentiated is that in which consciousness is lost through diffuse involvement of the brain in some toxic or infective process rather than through severe local damage to its structure. Loss of consciousness, the dominating event common to both groups, removes much of the evidence on which, in a conscious patient, one would rely to make the distinction. In these circumstances the doctor has to rely on prior knowledge of the patient, upon such history as is obtainable from third parties, and upon an objective examination akin to that in veterinary medicine.

Physical signs in an unconscious patient are difficult to elicit and treacherous to interpret. Any deeply unconscious person is likely to have a congested and cyanotic appearance and to breathe stertorously. The respiration may be rhythmic, but Cheyne-Stokes breathing is particularly common in apoplexy, and when associated with blowing out of one corner of the mouth it is very suggestive of unilateral brain damage. The pupils in unconscious patients are often inactive, and may be dilated or constricted. Marked inequality in size or dissimilarity in reaction between the two pupils indicates local brain damage. In any deeply unconscious person the limbs may be flaccid, the tendon reflexes absent, and the plantar responses extensor, but even in the absence of any co-operation it may be possible to demonstrate a marked difference between the two sides of the body, and this is a point in favour of apoplexy. Fits may occur, though they are more common when there is local brain damage, and they may leave behind them transient signs which are apt to confuse the issue. Incontinence of urine or faeces may occur in any unconscious patient and is of no diagnostic assistance. Ophthalmoscopic examination may provide critical information. Advanced papilloedema indicates raised intracranial pressure of some standing and does not make its appearance in a matter of hours, though in subarachnoid haemorrhage it may develop in a day or two. Hypertensive retinopathy is readily recognizable and should direct attention immediately to the cardiovascular system. Diabetic retinitis can be pathognomonic of that disease.

After the nervous system has been examined attention should next be directed to the cardiovascular system. A high systolic pressure—200 mm. Hg or over—is not by any means proof that the patient's illness is due to hypertension. This, and even a raised diastolic pressure, may be the result of increasing intracranial pressure, but a diastolic tension of over 120 mm. Hg is strong evidence of pre-existing hypertension. The heaving apex beat displaced to the left, which is so characteristic of left ventricular hypertrophy, is the best confirmatory evidence that hypertension is of long standing.

A specimen of urine should be examined as soon as possible. It is often necessary to pass a catheter to obtain it and time may have to be allowed if the patient has recently been incontinent. Glycosuria and even ketonuria are not by themselves proof of diabetes. The former may be found as a transient event in any acute cerebral disaster and the latter may occur after vomiting. But in these circumstances the amounts are usually small. Heavy albuminuria is strong evidence of kidney disease, but light albuminuria and fever may occur in any comatose patient.

The odour of the breath should always be noted, and may reveal the presence of ketosis, uraemia, or alcohol. The head should be examined for evidence of injury.

An assessment of these clinical observations will usually enable the physician to recognize those cases in which loss of consciousness is due to apoplexy, even in the absence of a clear history. The latter, when available, will usually put the matter beyond doubt. The reader is referred to the article in this series by Dr. M. J. Parsonage* for a consideration of the differential diagnosis of other causes of coma such as exogenous and endogenous intoxications, head injuries, and epilepsy.

Cerebral Embolism

The great majority of cases of apoplexy are caused by one of the three varieties of major cerebral vascular accident—embolism, thrombosis, or haemorrhage.

Of all varieties of apoplexy, that due to a massive cerebral embolism is the most sudden in onset. The patient may fall in his tracks as if pole-axed. The stroke is likely to occur during activity, and the damage to cerebral function, including loss of consciousness, reaches its height immediately. If the patient survives the next twenty-four to forty-eight hours, improvement is likely to set in.

A smaller embolism may produce only transient or minor symptoms, but may set up a retrograde thrombosis of the vessel proximal to the obstruction, leading to a major apoplexy of thrombotic origin when the lumen of such an artery as the middle cerebral or even the internal carotid becomes occluded.

British Medical Journal, 1955, 1, 217.

Apart from these features cerebral embolism can usually be suspected by the presence of a recognizable source of emboli. Of these, a diseased heart is the most important. Embolism may result from chronic mitral disease with or without auricular fibrillation; from fibrillation, however caused; from infective endocarditis; or from detachment of portions of a mural thrombus after myocardial infarction. Rarely, a fragment of clot may be detached from an atheromatous ulcer in the lumen of the aorta or the common or internal carotid arteries, and under special circumstances both fat and air may give rise to cerebral emboli.

Cerebral Thrombosis

Cerebral thrombosis is usually ingravescent in onset, occurring particularly during sleep, at rest, in the presence of debilitating circumstances such as minor illnesses, fatigue, exposure to cold, or in states of privation. It is the commonest cause of apoplexy in the aged and it is not uncommon in the middle-aged. In most cases its essential cause is atheroma of the cerebral arteries, but the occurrence of a cerebral thrombosis in a person under 40 should always bring to mind the possibility of syphilis. Rare causes of cerebral thrombosis are the different varieties of arteritis, such as polyarteritis nodosa and thrombo-angiitis obliterans, and certain of the blood diseases such as polycythaemia.

In all such cases thrombosis may be precipitated by any circumstance leading to a slowing of the cerebral circulation. Some degree of consciousness is commonly retained throughout the episode, or, if consciousness is lost, the resulting coma develops gradually. The neurological picture conforms to a recognized pattern depending upon the identity of the vessel occluded—for example, the middle cerebral, the calcarine, or the posterior inferior cerebellar arteries. Because the patient is able to co-operate, it is often possible to observe the neurological signs with accuracy. The cerebrospinal fluid in cerebral thrombosis, as in embolism, is under normal pressure and is usually normal in composition. If the resultant softening reaches the superficial or ventricular surface of the hemisphere the fluid may contain an increased amount of protein and an excess of cells, of which up to 50% may be polymorphs.

In cases of thrombosis a general medical examination will usually disclose evidence of generalized atheroma. Often, though by no means invariably, there is an associated hypertension and occasionally evidence of renal impairment. But atheroma is essentially a patchy disorder, and just as the coronary arteries may be prematurely affected in one individual, so the cerebral arteries may be prematurely affected in another. For this reason lack of evidence of generalized atherosclerosis does not exclude the diagnosis of cerebral thrombosis from this cause.

Intracranial Haemorrhage

Apart from the two varieties of traumatic meningeal haemorrhage—that is, extradural and subdural haemorrhage—which do not fall within the scope of this article, spontaneous intracranial haemorrhage may be intracerebral or subarachnoid in position. Either may occur in the absence of the other, but if the bleeding is severe a primary intracerebral haemorrhage usually leads to effusion of blood into the subarachnoid space, and a severe subarachnoid haemorrhage is often accompanied by a tearing up of the brain tissue and the consequent development of an intracerebral clot.

In the middle-aged or elderly patient intracranial haemorrhage provides the most classic example of apoplexy. A plethoric, hypertensive subject, or a person known to be suffering from chronic renal disease or other disorder associated with hypertension, is suddenly stricken while in the active pursuit of his normal affairs. Brief, agonizing headache, often associated with vomiting, quickly gives way to deepening coma with stertorous breathing and flaccidity on one side of the body. When first seen all reflexes are commonly absent, and deepening congestion may lead to death within half an hour of the first warning of disaster. The occurrence of neck stiffness may suggest the presence of blood in the subarachnoid space. Lumbar puncture in such a case usually yields a freely blood-stained fluid, indicating that the haemorrhage has burst through the superficial or ventricular surface of the brain. When this occurs death is seldom delayed beyond a day or so.

It is often supposed that survival after an intracerebral haemorrhage is rare and that those individuals who recover are more likely, in reality, to have suffered from a thrombosis. This viewpoint has probably been overstressed, and post-mortem examination as well as the results of surgical investigation of selected cases indicate that survival after massive intracerebral haemorrhage is by no means uncommon.

In healthy persons under the age of 35 intracranial haemorrhage is the most important cause of apoplexy and is usually predominantly if not entirely subarachnoid in type. Such disasters begin with sudden intense pain in the occipital or fronto-occipital regions, often accompanied by vomiting, followed rapidly by stupor and then coma. The patient on examination shows a varying combination of drowsiness and irritability, ranging from unrousable coma on the one hand to uncontrollable excitement on the other. Signs of meningeal irritation are prominent, but those of massive damage to the brain are often conspicuous by their absence. The optic fundi often show numerous recent haemorrhages, some of them subhyaloid. The C.S.F. is freely bloodstained and classically yields, on standing, a canary-yellow supernatant fluid. Such "spontaneous" subarachnoid haemorrhage is usually easily recognized, and in a previously healthy person it is almost invariably due to the rupture of some pre-existing vascular anomaly.

Since the recognition thirty years ago of the important part played by congenital berry aneurysms of the circle of Willis in the aetiology of spontaneous subarachnoid haemorrhage, it has become usual to attribute all such haemorrhages to the rupture of one of these structures. Time has shown this view to be an over-simplification, and the increasing use of arteriography has made it clear that a considerable proportion of these cases, indeed a majority in patients under 20, result from the rupture not of a congenital aneurysm but of a so-called angiomatous malformation. These peculiar structures, long recognized as occurring chiefly in the cerebral hemispheres, are evidently far commoner than was suspected before the days of arteriography. They consist of a tangle of thin-walled blood channels fed by one or more arteries of considerable size and draining into the neighbouring dural sinuses by thin-walled vessels often as large as one's little finger. They are not angiomas in the sense of being true neoplasms, but are vascular anomalies, almost certainly congenital in origin, which continue to develop as life advances. Clinically, these cases may present with epilepsy or migraine, often with rather atypical features; with progressive damage to the brain or with sudden subarachnoid or intracerebral bleeding following rupture. Frequently, though not invariably, such structures may be associated with a bruit audible on auscultation of the skull.

The distinction between a ruptured aneurysm and a ruptured angiomatous malformation as the cause of a spontaneous subarachnoid haemorrhage in a young person is always difficult and, by clinical means, often impossible. In the majority of cases the cause can be established with certainty only by arteriography, and this important subject is referred to below.

Rarer Causes of Apoplexy

Three relatively rare causes of apoplexy still need brief consideration—namely, the apoplectiform episodes of hypertensive encephalopathy, the congestive attacks of general paresis, and cerebral tumours.

Hypertensive Encephalopathy.—Patients suffering from extreme degrees of hypertension, whether primary or secondary in origin, are liable to recurrent episodes of cerebral disorder suggestive of a major cerebral vascular catastrophe, but which clear up in the course of a few days without serious sequelae. Such incidents rarely occur with a diastolic pressure of less than 130 mm. Hg, and become more frequent as the diastolic tension mounts towards 150–160 mm. Hg. They are usually preceded for a day or two by increasing drowsiness, mental confusion, headache, and sometimes vomiting. Examination may reveal a hemiplegia, monoplegia, dysphasia, hemianopia, or even total loss of sight. A serious vascular accident is suspected, but gradually during the course of a week or ten days the symptoms subside, consciousness returns, the evidence of local brain damage recedes, and the patient's condition reverts to what it was before the incident. The precise nature of the change in the brain during these episodes is unknown, but their transitory nature suggests that oedema rather than coarse changes in the circulation is responsible.

General Paresis.—It has long been known that the clinical course of G.P.I. may be punctuated by the occurrence of acute apoplectiform incidents which have been called "congestive attacks." Loss or severe impairment of speech is a common symptom in such attacks and may or may not be associated with a paresis of the face and arm or with frank hemiplegia. Mental confusion is the rule and consciousness may be diminished or lost. Recovery is usual in the course of a few days, but the patient is commonly left with increased mental impairment after each such episode, and the tremulous dysarthria so characteristic of G.P.I. is particularly in evidence after such episodes.

Cerebral Tumours.—Finally, a word needs to be said about cerebral tumours presenting in the guise of apoplexy. Generally speaking the clinical history of a case of cerebral tumour is one of gradual evolution, but occasionally acute episodes occur which may obscure the characteristic history, or may even be the first symptom of the illness. Such incidents are particularly common with secondary deposits of carcinoma from a primary growth in the bronchus, but may occur in other secondary growths as well as in the rapidly growing gliomas of elderly people. This possibility calls for a careful review of the history in atypical cases of apoplexy, with a view to eliciting previous symptoms suggestive of a cerebral tumour.

General Management

In days gone by the treatment of apoplexy resolved itself into the general management of the case with a view to preserving life and minimizing the effects of the permanent damage to the brain resulting from the stroke. There was no curative or preventive treatment. While modern advances have not made these general measures any less necessary, they have introduced possibilities both of improvement and of prevention that require discussion.

The immediate management of a case of apoplexy is that which applies generally to any unconscious patient. Where possible the trunk should be supported on pillows and the head should be turned to one side to minimize the risk of aspiration of stomach contents and secretions. Suction may be needed to keep the airway free, and initially nasal feeding is often necessary.

Attention to the back and hips to prevent bed-sores is that appropriate to any unconscious and doubly incontinent patient. Antibiotics may play a valuable part in the prevention and relief of chest infections.

As soon as consciousness has returned and the patient is able to co-operate, all joints of the affected limbs should be put through a full range of passive movements several times a day to minimize the danger of the development of "frozen" joints. In elderly subjects this risk is greatest in respect of the hip and shoulder. The wrist and ankle should be supported when at rest in postures of physiological dorsiflexion, but splints should be avoided, as they promote fixation. As soon as voluntary movement is regained in any part it should be vigorously encouraged by both nurses and relatives as well as by the skilled physiotherapist by means of active movements under supervision and of occupational therapy.* The patient should be got up into a chair as soon as possible after it is clear that natural recovery has begun, and attempts at walking should be started within a day or two of the patient being out of bed. Electrotherapy has no useful part to play in the treatment of such cases, and it is doubtful if any form of actinotherapy has more than a psychological effect.

In addition to these general measures, which are applicable to all recovering cases of apoplexy, modern therapeutic advances have introduced at least three possibilities of more active treatment which require consideration in appropriate cases. These are: (*a*) the treatment of the underlying hypertension in cases where hypertensive disease is the cause of the stroke, (*b*) the use of anticoagulants in cases of cerebral thrombosis and embolism, and (*c*) surgery in cases of subarachnoid and intracerebral haemorrhage.

Treatment of Arterial Hypertension

In many cases apoplexy is no more than an event in the evolution of the underlying disorder of essential or symptomatic hypertension, and in cases that survive the remote prognosis is that of the underlying disease.

The treatment of hypertension is at present in a phase of active evolution. In the past ten years thoraco-lumbar sympathectomy, hypotensive drugs, especially the methonium compounds, salt-free diets, and total adrenalectomy have all claimed attention. In a disorder so liable to natural fluctuations in intensity and so long drawn out in its evolution as essential hypertension, it is not possible yet to arrive at any final decision on the best treatment. However, in cases where cerebral vascular accidents have already occurred a decision for or against treatment has often to be taken without delay, and for this reason certain provisional, if purely personal, conclusions appear to be permissible. In severe cases of hypertension, whether essential or symptomatic, any measure which effectively reduces the blood pressure, as for example nephrectomy in unilateral pyelonephritis, is likely to be followed by a gratifying improvement in the general cerebral symptoms of hypertension and by a reduction of the liability to further cerebral damage. In the commoner cases where at best treatment can hope only to achieve an improvement in the blood-pressure level without reducing it to normal limits, the cerebral symptoms are among those which undergo the greatest degree of amelioration, and I have seen nothing to make me think that the risks of thrombosis with a lower pressure exceed the dangers of haemorrhage with a higher one. I therefore conclude that in a given case of essential hypertension the occurrence or threat of a cerebral vascular accident should be regarded as an encouragement rather than as a contraindication to active treatment of the underlying arterial hypertension.

Anticoagulants in Cerebral Thrombosis and Embolism

The introduction of anticoagulants suitable for prolonged administration and their proved value in the results of coronary artery disease naturally raises the question of their possible usefulness in combating the results of cerebral vascular disease.

Theoretically, it is possible to envisage a number of advantages and disadvantages of such treatment. Anticoagulant therapy should decrease the liability to further thrombosis of the cerebral vessels in threatened persons, as in cases of coronary occlusion, but in the case of the brain the risk of haemorrhage exists which does not exter the picture in cases of myocardial infarction. Further, the danger of an extension or recurrence after a cerebral thrombosis is much less than after a coronary occlusion, and the differential diagnosis between a cerebral thrombosis and an intracerebral haemorrhage is often in doubt. Possibly from these

*For further details see under "Any Questions?" at p. 1220, the answer on physiotherapy after a stroke.

considerations, possibly from native conservatism, anticoagulant therapy does not seem to have been extensively employed in this country.

Surgery in Cerebral Haemorrhage

The introduction of cerebral angiography has made possible a precision in the diagnosis of certain cerebral vascular accidents which could never have been achieved by purely clinical means, and with this improvement in diagnosis has come the possibility of direct attack on the source and results of intracranial haemorrhage.

Angiography was first applied to the investigation of cases of spontaneous subarachnoid haemorrhage. Although it has long been possible to diagnose such cases with reasonable certainty, and although it was recognized that they were due in many cases to the rupture of a pre-existing anomaly, it was seldom possible to determine with accuracy the position of the offending aneurysm or angioma, and in consequence treatment could only be supportive. Now it is possible in many cases to visualize small aneurysms on the component vessels of the circle of Willis or on the middle or anterior cerebral arteries, and in suitable cases these may be eliminated surgically or the dangers of a further haemorrhage may at least be reduced by ligation of the appropriate carotid artery.

One of the surprising results of angiography as applied to a large number of cases of subarachnoid haemorrhage has been to show how many of these cases, particularly in adolescents and young adults, result from bleeding from angiomatous malformations rather than from aneurysms. These vascular anomalies usually lie on the surface of the brain and are eminently suitable for surgical removal. When once they are removed, the liability to recurrent bleeding is slight, as, unlike aneurysms, they are solitary. One thus reaches the conclusion that every case of subarachnoid haemorrhage in a young person without hypertension should be submitted to full investigation, including cerebral arteriography, as soon as possible after the initial haemorrhage. It is well to remember that there is often only a short interval between the initial bleeding and a subsequent one that may be fatal.

Nor is it only in cases of subarachnoid bleeding that modern methods of neurosurgical and neuroradiological investigation have introduced the possibility of more active treatment. The same is true of intracerebral haemorrhage. Regular study of post-mortem material makes it clear that many patients survive intracerebral haemorrhages of moderate size, provided these do not rupture into the ventricle or through the surface of the brain. Such haemorrhages give rise to intracerebral clots which separate the cortex from the underlying white matter or split the white matter apart without necessarily destroying its fibres.

It has been contended by various workers that the early evacuation of such clots permits a degree of recovery of function much greater than would occur if the clots were left to resolve by the natural processes of liquefaction and absorption. With this view I am in agreement. The practical application of this viewpoint clearly requires that we should be able to recognize cases of intracerebral haematoma and particularly to distinguish them from ischaemic softenings; on purely clinical grounds this is always difficult and often impossible. The associated circumstances, the mode of onset of the stroke, and the shape of the cerebral lesion may all give important indications, but are seldom sufficient to decide with certainty between a softening and an intracerebral haemorrhage in an elderly hypertensive subject. On the other hand, shift of the pineal shadow, deviation of the midline arteries towards the hemiplegic side, and distortion of the ventricular system may together give indisputable evidence of an intracerebral haemorrhage under tension and so justify an operation to evacuate the clot.

Such investigations can only be carried out in hospitals specially staffed and equipped, and a moment's reflection will make it clear that the acceptance of the viewpoint expressed here will create a practical problem of considerable magnitude. However, it is one from which we should not shrink if careful and controlled study confirms that the degree of recovery in cases of intracerebral haemorrhage is thereby improved.

Conclusion

The main purpose of this article has been to advocate a more critical and constructive attitude towards the subject of apoplexy. This condition is one of the chief causes of death and disabling illness after middle age, and year by year its toll increases.

It must be feared that for the foreseeable future this will continue to be the case, but modern methods provide us with means of dealing effectively at least with the fringe of the problem. The first requirement, if such methods are to be employed, is that cases suitable for investigation and possibly for specialized treatment should be separated from those that are unsuitable.

This demands accurate diagnosis, which, in the nature of the problem, must initially be made in the patient's own home by those in general practice.

Next article on Emergencies in General Practice.—"Acute Psychosis," by Drs. J. Harrington and W. Mayer-Gross.

Refresher Course Book.—Copies of the second volume of collected articles from the Refresher Course for General Practitioners are still available at 25s. (postage 1s.) each. The first volume is now sold out.

Clinical Pathology Book.—"Clinical Pathology in General Practice," a collection of 39 articles on clinical pathology that appeared in the *Journal* as part of the Refresher Course for General Practitioners, is now available, price 21s. (postage 9d.).

Both these volumes are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1, or through any bookseller.

VISIT OF THE RUSSIAN DOCTORS

The six distinguished Russian doctors who have been visiting Britain as guests of the British Medical Association concluded their three-week tour on Tuesday, November 8, when they left by plane for Russia.

London

The tour opened with the luncheon at B.M.A. House on Monday, October 17, at which Dr. E. A. GREGG, chairman of the B.M.A. Council, welcomed the visitors (see this *Journal*, October 22, p. 1021). At a reception at the Royal Society of Medicine that evening the president, Sir WILLIAM GILLIATT, received them. Most of the next day was spent at the Postgraduate Medical School at Hammersmith. Professors JOHN MCMICHAEL and IAN AIRD were guides, and Sir DESMOND MORTON, chairman of the board of governors, presided at luncheon. In the evening London University gave a dinner in honour of the visitors, the vice-chancellor, then Professor HAROLD ROBINSON, presiding. On Wednesday (October 19) the guests were received at the Wellcome Foundation's museums and laboratories in the Euston Road by Mr. M. W. PERRIN, chairman of the Foundation, and Sir HENRY DALE, chairman of the Wellcome Trustees. At the luncheon given by the Society of Apothecaries at their Hall in Black Friar's Lane, the master, Dr. N. S. FINZI, was host. The party then divided, some going to see the Glaxo Laboratories at Greenford, some to the surgical unit at St. Mary's Hospital, and some to the Chester Beatty Research Institute at the Royal Marsden Hospital. The National Institute for Medical Research at Mill Hill was visited on Thursday (October 20), where the director, Sir CHARLES

HARINGTON, entertained the Russians to luncheon and tea; Professor LARIONOV was Dr. J. CRAIGIE'S guest at the near-by Laboratories of the Imperial Cancer Research Fund. In the evening there was a dinner at Lancaster House given by Her Majesty's Government, with the Minister of Health, Mr. IAIN MACLEOD, in the chair. On Friday (October 21) Professor B. W. WINDEYER (the dean) and Brigadier G. P. HARDY-ROBERTS (secretary-superintendent) showed the party round the Middlesex Hospital. Luncheon at the Royal College of Surgeons, with Mr. JULIAN TAYLOR, the senior vice-president, as host, was followed by a short tour of the College buildings. After that visits were paid by individual members to the Wright–Fleming Institute at St. Mary's Hospital, University College Hospital, the Elstree Laboratories of the Lister Institute, and elsewhere. The evening was given to relaxation. The male members were taken to the musical show "Kismet" and on to the Savoy Hotel as guests of the College of General Practitioners; the ladies dined at the Royal Festival Hall with the Medical Women's Federation. On Saturday excursions were made to Osterley Park and to Windsor Castle. On Sunday the party left by air for Edinburgh.

Scotland

The Russians were met at the airport by Dr. J. G. M. HAMILTON and Dr. GEORGE IRELAND, members of Council of the B.M.A., and by Dr. E. R. C. WALKER, the Scottish Secretary. They spent their first day in Edinburgh visiting individually the University departments of medicine, surgery, therapeutics, neurosurgery, pathology, materia medica, and natural history, as well as the Northern General Hospital and the Western General Hospital; they lunched as guests of Edinburgh University with Sir EDWARD APPLETON, the principal. They were received at the Department of Health for Scotland by Mr. J. NIXON BROWNE, M.P., Joint Under-Secretary of State for Scotland, Mr. H. R. SMITH, secretary of the department, and Dr. H. KENNETH COWAN, chief medical officer. The president, Professor WALTER MERCER, and council of the Royal College of Surgeons of Edinburgh gave a cocktail party, which was followed by dinner at the Royal College of Physicians of Edinburgh, where Sir STANLEY DAVIDSON, the president, welcomed the visitors.

After sightseeing in Edinburgh the party took a morning train to Glasgow, where they were met by Dr. I. D. GRANT, chairman of the Representative Body of the B.M.A., Dr. W. M. KNOX, chairman of the Scottish Committee, and Dr. J. T. MCCUTCHEON, of the B.M.A.'s Glasgow office. They were guests of the LORD PROVOST OF GLASGOW for luncheon at the City Chambers. In the afternoon visits were paid to the Royal Infirmary, the Western Infirmary, the Royal Beatson Memorial Hospital, and to the Blood Transfusion Unit. Professor SARKISOV went to Glasgow University, where he was received by Professor R. C. GARRY and Professor T. FERGUSON RODGER. In the evening there was a reception at the Royal Faculty of Physicians and Surgeons of Glasgow at which the president, Professor STANLEY GRAHAM, received the guests, followed by a dinner given by the B.M.A. at the New Club, where Dr. I. D. GRANT and Dr. W. M. KNOX were hosts. The next morning (Wednesday, October 26) was spent visiting hospitals; in addition to those seen the day before some of the party also went to Killearn Hospital. The University of Glasgow and its principal, Sir HECTOR HETHERINGTON, gave a luncheon for the visitors, at which Professor T. FERGUSON presided, and in the afternoon there was a trip down the Clyde. The Scottish part of the tour ended with a reception and film show at the Association's Glasgow office, at which Dr. I. D. GRANT presided.

Birmingham

On Thursday, October 27, the visitors went to Birmingham. Professors SARKISOV and GAUSE left the main party for the day, the former to visit the Burden Neurological Institute at Bristol under Dr. W. GREY WALTER, the latter to visit the Medical Research Council's antibiotics research station at Clevedon, Somerset. The main party went to the Queen Elizabeth Hospital, where they were received by the chairman of the hospital committee, Mr. HAMILTON BAYNES, and the matron, and they were conducted to the hospital's various departments by Professors F. A. R. STAMMERS and H. C. MCLAREN. After lunch at the Queen Elizabeth, the chairman of the board of governors (Mr. E. A. NORTON) presiding, the party went to Stratford-on-Avon, to be shown the sights by Dr. A. MURRAY, who provided tea. In the evening in Birmingham they were received at a cocktail party by Dr. MATTHEW BURN (chairman of the B.M.A. Division) and Dr. J. K. H. MCCULLOUGH (joint hon. secretary). The LADY MAYORESS was present, and the guests included Drs. GUY DAIN, S. WAND, and J. A. BROWN. The next day the visitors went to the Midland Centre for Neurosurgery at Smethwick, where they were received by the chairman of the regional hospital board (Mr. V. W. GROSVENOR) and the matron. They were taken round the hospital by Mr. J. M. SMALL, Dr. A. L. WOOLF, and Dr. E. R. BICKERSTAFF. A reception by the LORD MAYOR and LADY MAYORESS (Alderman and Mrs. A. Lummis Gibson) was followed by luncheon. In the afternoon the party split into two, Professor KOVANOV and Dr. BOGOMOLOVA going to the Birmingham Accident Hospital, where they were shown round by the director, Mr. W. GISSANE, the others visiting the medical school, where they were received by the sub-dean, Professor C. F. V. SMOUT, and toured the various departments. In the evening the visitors had dinner with the dean of the medical faculty, Professor A. P. THOMSON, when the vice-chancellor of the University, Dr. R. S. AITKEN, was present. They also visited the homes of Drs. M. BURN, F. E. GOULD, and J. K. H. MCCULLOUGH.

Cambridge and Oxford

The final week included two-day visits to the Universities of Cambridge and Oxford. Arriving at Cambridge on Saturday evening (October 29), the party began Sunday by attending matins at King's College Chapel, and afterwards were shown round Trinity by the master, Lord ADRIAN. Luncheon was taken with Dr. and Mrs. H. R. YOUNGMAN at their home. The Cambridge Division of the B.M.A. were the hosts for dinner, Dr. ALEXANDER BROWN being in the chair. Among those present were Sir LIONEL WHITBY, regius professor of physic, Lady WHITBY, and the MAYOR and MAYORESS of Cambridge. On Monday, October 31, the guests visited the department of human ecology, where Sir ALAN ROOK and Professor A. L. BANKS entertained them. Then they divided to visit the departments of medicine, radiotherapy, anatomy, and physiology, the blood transfusion service, and Medical Research Council units, meeting again for luncheon at Downing College, where they were entertained by the master, Sir LIONEL WHITBY. In the afternoon most of the visitors went on an excursion to the Papworth Village Settlement, where Dr. R. R. TRAIL showed them round. Later the vice-chancellor of the University, Professor B. W. DOWNS, held a reception at Christ's, and this was followed by dinners at Trinity, Downing, or Girton.

On Tuesday, November 1, the party left for Oxford, on their arrival lunching with the Oxford Division of the B.M.A., with Dr. J. N. P. HEWLINGS in the chair. After Professor A. D. GARDNER had welcomed the Russian visitors, Dr. J. M. WALKER then conducted the party to the Bodleian Library, where a fine display of Russian books and MSS. had been prepared, to Magdalen, where Pavlovian relics were on display, and then to tea at Christ Church. The vice-chancellor, Professor A. H. SMITH, entertained the party to a dinner at New College, at which were present Sir W. LE GROS CLARK, Dr. JANET VAUGHAN, and Professor L. J. WITTS. The last day at Oxford, Wednesday, November 2, was spent in visits to various departments in the Faculty of Medicine. Luncheon was at the Radcliffe Infirmary with Sir DAVID KEIR, chairman of the board of governors, followed by a tour of the various clinical departments. The party were then shown demonstrations at the Nuffield

Institute for Medical Research by the director, Dr. G. S. DAWES. Professor FOTEEVA spent the morning in visiting the Atomic Energy Research Establishment at Harwell. The party returned by an evening train to London.

Final Engagements

On Thursday, November 3, Professor LARIONOV lectured in the morning at the Chester Beatty Research Institute at the Royal Marsden Hospital. This was followed by a luncheon at the Royal College of Physicians of London, where Sir RUSSELL BRAIN, the president, received the guests. In the afternoon Professor KOVANOV demonstrated to Professor C. G. ROB, of St. Mary's, his special apparatus for suturing arteries. Afterwards Professor KOVANOV talked to a large audience of students about medical students in Russia. In the evening there was a reception at the Soviet Embassy, at which Professor SARKISOV received the guests.

On the last day of their formal programme, Friday, November 4, the visitors met the Council of the B.M.A. in session at B.M.A. House. In the evening they were guests of honour at the Council dinner. These events are described elsewhere (*Supplement*, p. 119). In addition, the Russian doctors also attended a reception by the British Red Cross Society in the afternoon, where they were received by Lord WOOLTON, chairman of the executive committee. Earlier Professor SARKISOV and his colleagues had given their impressions of their tour to a press conference.

The Association is much indebted to those who helped to make this visit such a successful one, and in particular the officers and secretaries of the Divisions and Branches of the B.M.A. in the various towns and cities mentioned above.

Nova et Vetera

MEDICAL ANCESTOR OF H.R.H. PRINCE CHARLES, DUKE OF CORNWALL

It is not widely known that the Heir Apparent to the Throne, whose birthday is on November 14, has among his ancestors a member of the medical profession in the person of Leopold Lafontaine.

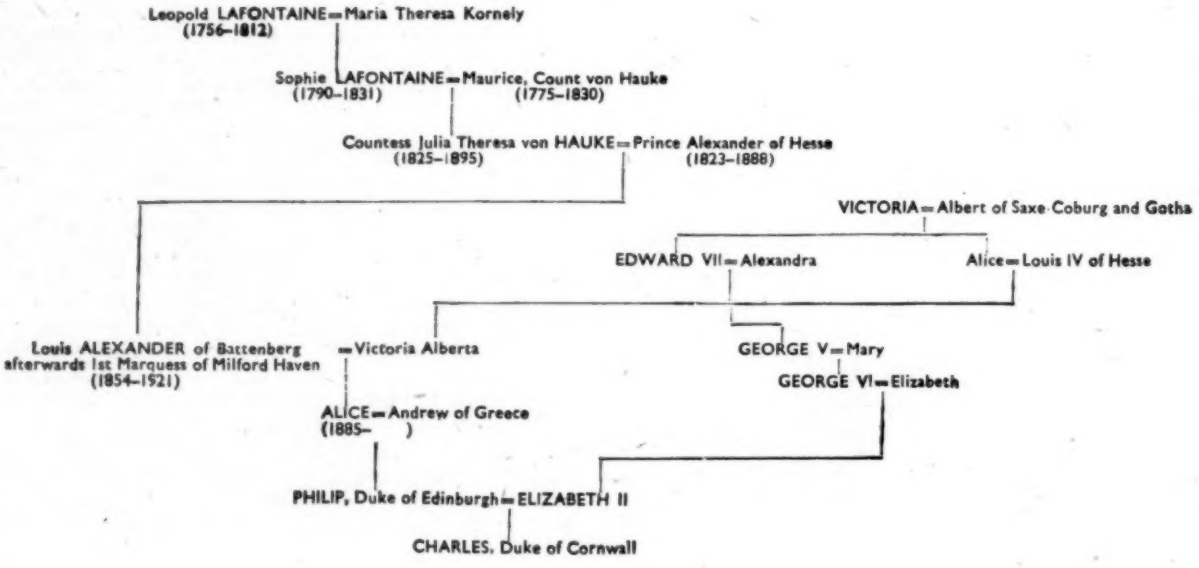
Franz Anton Leopold Lafontaine, born at Biberach, Germany, in 1756, was the son of Benno Leopold Ignatius Lafontaine, merchant (baptized at Biberach, June 17, 1731), by his wife, Maria Katherina Franziska Leonhardt (baptized at Biberach, October 5, 1725), whose marriage took place at Biberach on November 25, 1753. It is possible that the Lafontaine family was descended from a Huguenot refugee.

Leopold Lafontaine studied medicine at Strasbourg, and after qualification settled at Krakow, Poland, where he became one of the leading surgeons. He took a great interest in the creation and administration of the spa at Krzeszowice, about which he wrote a monograph (in Polish) in 1789. In 1787 he was appointed physician to Stanislaus II, King of Poland, and served also as a privy councillor. Joseph Poniatowski, nephew of Stanislaus II, and commander-in-chief of the Polish army, who had gone into exile after the partition of Poland and had returned to take part in the Kosciuzko rising of 1794, had, after the Battle of Jena, been appointed head of the Polish National Guard. During his reorganization of that body he appointed Lafontaine surgeon-general of the Polish army medical corps. During the Russian campaign of 1812, in which the Polish forces fought on the side of Napoleon, Lafontaine was taken prisoner. He died in captivity at Mogilev, on the Dnieper, on December 12, 1812.

Lafontaine wrote *Chirurgische-medicinische Abhandlungen*, 1792, from which the treatise on plica polonica ("Polish plait") was translated into French by A. J.-L. Jourdan, 1808. He was also the founder and editor of a monthly medical journal, *Dziennik Zdrowia*, 1801–2. A collection of his *Hinterlassene vermischte medicinische Schriften* was published in Breslau, 1824, and this includes a memoir by J. R. Lichtenstädt.

Lafontaine married Maria Theresa Kornely, of whom I have no other knowledge but would welcome further particulars. Their daughter Sophie, born at Warsaw in 1790, married Maurice, Count von Hauke, sometime Polish War Minister and a general of artillery, on September 27, 1807. She died at Warsaw on August 27, 1831. Sophie bore eleven children, the tenth being Julia Theresa, born at Warsaw on November 12, 1825, died at Heiligenberg on September 19, 1895. Countess Julia von Hauke was morganatically married on October 28, 1851, to Prince Alexander of Hesse (1823–88), younger son of Louis II, Grand Duke of Hesse-Darmstadt. Their son, Prince Louis of Battenberg, afterwards first Marquess of Milford Haven (1854–1921), married his cousin, Princess Victoria Alberta (1863–1950), daughter of Louis IV of Hesse-Darmstadt and a granddaughter of Queen Victoria. Their eldest child, Princess Alice, was born in 1885 and married the late Prince Andrew of Greece, their youngest child being Prince Philip (H.R.H. the Duke of Edinburgh), born 1921. Prince Charles, Duke of Cornwall, was born in 1948.

B. BUCKLEY.


Leopold LAFONTAINE = Maria Theresa Kornely
(1756–1812)
Sophie LAFONTAINE = Maurice, Count von Hauke
(1790–1831) (1775–1830)
Countess Julia Theresa von HAUKE = Prince Alexander of Hesse
(1825–1895) (1823–1888)
VICTORIA = Albert of Saxe-Coburg and Gotha
EDWARD VII = Alexandra
Alice = Louis IV of Hesse
Louis ALEXANDER of Battenberg afterwards 1st Marquess of Milford Haven
(1854–1921)
= Victoria Alberta
GEORGE V = Mary
GEORGE VI = Elizabeth
ALICE = Andrew of Greece
(1885–)
PHILIP, Duke of Edinburgh = ELIZABETH II
CHARLES, Duke of Cornwall

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Epsom College Centenary Appeal

SIR,—About a year ago (*Journal*, November 27, 1954, p. 1280) you were good enough to print and to commend warmly to your readers the centenary appeal, sponsored by the council of the Royal Medical Foundation of Epsom College, for funds wherewith to carry out a carefully considered programme of new buildings and rebuilding necessary to maintain the high repute enjoyed by the College.

In reporting now the result of the first year's work of the Appeal Subcommittee we should like to remind the profession that at the very least £100,000 is required to enable the council to do what must be done, and that a further £50,000 is really necessary to complete the work. Towards this sum about £20,000 is now in hand, and seven-year covenants have been entrusted to us, the total value of which may reach a further £24,000. Only 1.5% of those to whom the appeal was issued—that is, the medical profession—have sent donations. It will be seen that the council has not quite reached half-way to its first target; and it does most earnestly beseech its professional colleagues who have not yet subscribed for generous help in its planned work.

Notwithstanding the good will and assistance readily given by the medical press, there seems to be still widespread ignorance among our profession of the benefits which Epsom College provides in the free education of medical orphans and in a first-class school at reasonable cost for the children of practising medical men and women. The Foundation needs many more honorary local secretaries throughout the kingdom to help in dispelling this lack of comprehension; and volunteers for this admittedly arduous task would be gladly welcomed by the council.

Meanwhile we do urgently plead both for more annual subscribers, and, at this moment especially, for donations towards our centenary appeal. We have reached a stage where we cannot go back and find it embarrassing to commit ourselves to building operations unless we have assured financial support. To all those who have already helped most grateful thanks are tendered. May we ask those who have not done so to send a donation now to the secretary, Epsom College, Surrey?—We are, etc.,

WEBB-JOHNSON, President.
HENRY ROBINSON, Treasurer.
RONALD W. RAVEN, Chairman.
HENRY FRANKLIN, Headmaster.
LAWRENCE PENDRED, President, Old Epsomian Club.

Epsom College, Surrey.

Infections in the Newborn

SIR,—I have just read your leading article on the above subject (*Journal*, July 9, p. 111), in which it is stated, "Pickerill, in New Zealand . . . has shown that hospital infection is almost eliminated when mothers can nurse their babies in separate rooms of their own . . . it would be quite impracticable for all maternity patients to nurse their babies away from all other patients and out of contact with hospital staff." But is it "quite impracticable"? Successful mother-nursing to avoid hospital infection depends primarily on structure. If a new building cannot be obtained, then an old ward can be subdivided into a number of small rooms, 10 ft. × 11 ft. (3 m. × 3.3 m.), at relatively small expense. The physical barrier of a door (with a glass window for observation) would be essential, also an electric bell or indicator for the mother's use. What to do whilst this was being done? That is up to the persuasiveness and drive of those who want it. Facilities for mother-nursing will not fall like manna from heaven.

When this is accomplished every baby can be left safely in its mother's room and removed for no purpose whatever. It is just possible that the "impracticability" is largely mental, which may be more difficult to alter than the ward. If there is one thing more than another which a nurse should be taught it is that she must *not* handle or feed babies when the mother, to whose organisms alone the baby carries immunity,[1] is available. She may do what is necessary for the mother but *not* for the baby. The communal nursery is undoubtedly the place where hospital infection occurs, therefore it should be eliminated, for it constitutes the same kind of danger as the handle of the Broad Street pump did 100 years ago. In a normal maternity case a mother while still in bed could soon feed, bath, and change napkins for her baby with avoidance of hospital infection and with benefit, both physical and psychological, to herself. Early absence of the latter may have a lasting and harmful effect. The above are the three points of danger where infection crosses. All the necessary utensils, including a small light bath, can be numbered (not with the ubiquitous bit of strapping) and kept in the mother's room of the same number, and only removed for sterilizing with immediate replacement. The mother would require only a nurse or aid to put things within reach and remove them after use.

Five other valuable assets would accrue: (1) It would then be possible to thoroughly clean and ventilate the room between occupants—surely most elementary hygiene, and of the greatest value in stopping the perpetuation of inhabitating organisms, but which is quite impossible in an open ward or a nursery. (2) There would be no communal particles floating in the atmosphere. (3) Nurses would not be overworked. (4) Less staff would be required. (5) The nursery could be turned into a room for a mother and baby. But possibly the greatest advantage would be found in the knowledge that if a serious infection did occur it certainly would not sweep through the unit like a fire. Here, in the Bassam Hospital, no infection has ever spread even to one other infant. These are the principles of insulation (not isolation, which is very different) of mother and baby which have been found so successful in this hospital—very simple but most effective.

Last but not least there would be no possible risk of a mother getting the wrong baby.—I am, etc.,

Wellington, New Zealand. CECILY M. PICKERILL.

REFERENCE

1 Murray, J., and Calman, R. M., *British Medical Journal*, 1953, 1, 13.

A Simple Blood-grouping Method

SIR,—Dr. R. A. Zeitlin (*Journal*, October 15, p. 970) raises some objections to the cards for ABO and Rh grouping mentioned by Mr. J. T. Rice-Edwards (*Journal*, September 10, p. 681), Dr. Philip Boyd (*Journal*, September 24, p. 793), and Dr. A. Ambery Smith (*Journal*, October 1, p. 850). In the publication referred to by Dr. Boyd,[1] Dr. Zeitlin could have found the answer to any of his objections now advanced, together with an account of more than 35,000 groupings on the cards. Of course, an ABO determination on the card can be supplemented with an investigation of the serum against known A and B cells, as done in approximately 20,000 cases. The card groupings are, however, practically independent of those possible sources of error which in other methods strongly indicates this serum check.

As to Dr. Zeitlin's experience with the French *hémobiotest rapide*, the sera of which became inert after a short time of storage, this cannot seriously be used as an objection to the Danish cards, proved to be stable for at least two years when stored at 20 or 37° C.—I am, etc.,

Copenhagen. KNUD ELDON.

REFERENCE

1 Eldon, K., *Dan. med. Bull.*, 1955, 2, 33.

Blood Groups and Disease

SIR,—The pioneer investigation of the incidence of the blood groups in diseases—that of Buchanan and Higley[1] in 1921, at the Mayo Clinic—had a significant excess of blood group O in its series of peptic ulcer cases.[2] The ratio of duodenal to gastric ulcer cases was 102:42—diagnosis of gastric ulcer was then less advanced—and now Dr. C. A. Clarke *et al.* (*Journal*, September 10, p. 643) have found a significant excess of group O in their duodenal but not in their gastric ulcer series. The latter study illustrates one method of investigating the subject, while Buchanan and Higley's data can be used for a rough-and-ready illustration, as is seen in Table I, of an alternative method recently described.[3] Table I shows the descending order of percentages of blood group A in the (very broadly) comparable disease groups of the Mayo Clinic study and the Finnish studies of Streng and Ryti,[4] Sievers,[5] and Mustakallio[6] combined. Table II shows the same in the Finnish workers' studies of diseases due to infection, and suggests[7] that investigation should be resumed while such diseases are still quite common.

TABLE I.—*Percentage of Blood Group A in Hospital Patients*

Data of Buchanan and Higley			Data of Finnish Authors		
Number of A Patients	Disease Group	Percentage of A Patients	Percentage of A Patients	Disease Group	Number of A Patients
301	Anaemias	43·5	49·5	Anaemias ..	145
119	Carcinoma	40·8	46·7	Malignancy	140
7	Heart ..	35·0	44·5	Heart ..	446
21	Kidney ..	33·9	42·2	Kidney ..	209
38	Blood ..	33·3	40·6	Blood ..	56
12	Thyroid ..	32·4	40·3	Thyroid ..	108

TABLE II.—*Percentage of Blood Group A in Hospital Patients*

Number of A Patients	Disease or Group of Diseases	Percentage of A Patients		
		Streng and Ryti	Sievers	Mustakallio
1,125	Tuberculosis	44·5	44·8	45·7
222	Rheumatic fever	—	42·8	43·5
451	Respiratory infections ..	39·9	41·3	42·4
907	Infectious diseases ..	31·0	41·1	40·9

By the use of Streng's[8] adaptation of an analogous graphic method Streng and Ryti[4] found a shortage (in every age group) of tuberculous group O patients (see, in addition, Rubashkin and Leiserman[9]), and by the same method Mustakallio[6] found a deficit of A in thyroid diseases and an excess of A in anaemias. These results were thought by the authors to be due, at least in part, to geographic variation in distribution alike of patients and of blood groups—the method partially exemplified in the tables would presumably get round this—and there has lately been given by Woolf[10] a more abstruse statistical reason why intra-national variation should be allowed for in the assessment of results. There may, however, be a genetic reason also, since if a disease were more common, for instance, in *AA* than *AO* individuals it would be relatively commoner in regions of high A incidence—other things, that is, being equal—as in these a higher proportion of A's would be *AA*. Furthermore, if a disease were more common in A_1 than in A_2 individuals the descending order of liability to that disease in A and AB individuals might, other things again being equal, be something like $A_1A_1—A_1A_2—A_1O—A_1B—A_2A_2—A_2O—A_2B$.

Age group and sex, too, may be important, as appears from the Maxwells's series of hypertensives (*Journal*, July 16, p. 179) mostly referred for venesection in their 60's. There is here a significant shortage of AB males (Aird *et al.*, *Journal*, July 30, p. 321), but in the donor series of Hart[11] and Fraser Roberts[12] there is also a shortage, albeit a non-significant one, of AB males over 50, and especially of those in their 60's. (The descending order of sex ratios of the other donors over the age of 50—namely O–A–B—is reversed in the Maxwell's series of hypertensives.) Such a shortage, if confirmed, would be consistent with the fact that in the study by Aird *et al.*[2] of four diseases the males with the lowest mean age were the AB's in all but one, and with their suggestion that hypertension may kill AB males at an earlier age than other people—a suggestion implying the reasonable assumption that hypertensives (and so an excess of hypertensive AB males) are not so likely to be referred for venesection in middle age as in their 60's. On the other hand, AB males may tend to be free of hypertension till an age when venesection might be harmful.

Such problems suggest that the method exemplified in the tables should be refined to deal with patients of different sexes and age groups as well as of different blood groups, and that on the other hand detailed comparison should be made of the medical *history* of people of each combination of age group, sex and blood group. Sources of data for this—a study of the incidence of diseases in the blood groups, as opposed to that of the blood groups in diseases—would be schoolchildren, National Service men, blood donors, blood-test subjects, general hospital out-patients, patients in paediatric, maternity, and geriatric hospitals, and necropsy subjects in every age group. Positive findings in child as well as adult populations would suggest that the ABO blood groups of none but the newborn could with safety be regarded as the norm, and as an index alike of regional variation and of secular change, if any. And in that case the ABO blood groups of newborn infants might well be added to the country's vital statistics.—I am, etc.,

Aberdeen. T. M. ALLAN.

REFERENCES

1 Buchanan, J. A., and Higley, E. T., *Brit. J. exp. Path.*, 1921, **2**, 247.
2 Aird, I., Bentall, H. H., Mehigan, J. A., and Roberts, J. A. Fraser, *British Medical Journal*, 1954, **2**, 315.
3 Allan, T. M., ibid., 1954, **2**, 644.
4 Streng, O., and Ryti, E., *Acta Soc. Med. "Duodecim,"* 1927, **8**, fasc. 6, 1.
5 Sievers, O., *Finska Läksällsk. Handl.*, 1929, **71**, 836.
6 Mustakallio, E., *Acta Soc. Med. "Duodecim,"* 1937, **20A**, fasc. 2, 1.
7 Kennaway, E. L., *British Medical Journal*, 1954, **2**, 663.
8 Streng, O., *Acta Soc. Med. "Duodecim,"* 1926, **8**, fasc. 1.
9 Rubashkin, W., and Leiserman, L. I., *Ukr. Zbl. Blutgr.*, 1929, **3**, 303.
10 Woolf, B., *Ann. hum. Genet. (Lond.)*, 1955, **19**, 251.
11 Hart, E. W., *Ann. Eugen. (Lond.)*, 1944, **12**, 89.
12 Roberts, J. A. Fraser, ibid., 1948, **14**, 109.

"The Private Pestilence"

SIR,—Any account (*Journal*, October 29, p. 1083), however cursory, of the early literature of puerperal fever which omits my ancestor Charles White's *Treatise on the Management of Pregnant and Lying-in Women* (London, 1773) must be considered woefully inadequate.

This work, which was published in Boston also in 1773, and was later translated into French and German, contains the following paragraph: "If separate apartments cannot be allowed to every patient at least as soon as the fever has seized one she ought immediately to be moved into another room not only for her immediate safety, but that of the other patients . . . whenever a patient has recovered from this fever and is removed to another room the bedding and curtains should be washed, the floor and woodwork cleansed with vinegar, and it would still add to the salubrity of the apartment if it were stoved with brimstone."

To what else does this advice amount than to a recognition of the contagious nature of puerperal fever? White claimed that he never lost a case of puerperal fever in a mother who was delivered without the aid of instruments. He preached personal cleanliness of the obstetrician and attendants, clean instruments and linen, and fresh air. He wrote 22 years before Alexander Gordon and 88 years before Semmelweis.—I am, etc.,

Newcastle-upon-Tyne, 2. W. G. A. SWAN.

Munchausen Syndrome

SIR,—I was interested to have further news of the patient described by Drs. R. A. Gawn and E. A. Kauffmann (*Journal*, October 29, p. 1068). I have often wondered if he was still doing the rounds of the hospitals, and have kept an eye open for him in those I have worked in.

There is in his case records in the Western Infirmary, Glasgow, a dossier of letters which I received from hospitals where he was known. His mobility was remarkable—within two days of his discharge in Glasgow he was admitted to a London hospital, and on another occasion he entered a hospital in the Midlands, having been discharged the same day from one in Kent. At that time he nearly always used the same name; I wonder if he still uses it. Dr. Asher,[1]

in his original article on Munchausen syndrome, used pseudonyms with a fairly obvious allusion to the real name of the patients. I believe that publication of the real name would be justifiable, in spite of ethical objections. Perhaps the *British Medical Journal* could publish a "rogues' gallery" for the better protection of hospitals and public funds.

As regards the source of blood, we satisfied ourselves that he obtained his supplies by scarifying his urethra with a pin. This incidentally produced convincing haematuria. Unless he has changed he can easily be persuaded to take his own discharge by the threat of cystoscopy, *verb. sap.*—I am, etc.,

Manchester, 13. IAN A. SHORT.

REFERENCE

1 Asher, R., *Lancet*, 1951, 1, 339.

SIR,—In their case report Drs. R. A. Gawn and E. A. Kauffmann (*Journal*, October 29, p. 1068) complain bitterly about a psychopathic malingerer who fooled them, and others before them, by pretending to suffer from some mysterious bodily illness when, in fact, he did not so suffer. The authors conclude: "This patient will undoubtedly remain a constant nuisance, and any doctor having to treat him in future should consider the desirability of certification. The cost to the Health Service of his innumerable admissions to hospital and exhaustive investigations on each occasion must be fabulous."

But all the rumpus and cost to the Health Service were caused by the many doctors who ordered expensive investigations and treatment, and not by the patient, who merely, and quite lawfully, presented to his medical advisers with a tall story and a blood-stained face. That his medical advisers got hold of the stick by the wrong end, and only after many laborious, useless, and costly investigations came to the right psychiatric diagnosis, is not his fault. He and his predecessors in the Munchausen game did, in fact, not suffer from Munchausen, but from misdiagnosis. So why certify him?

Had the Hess's test been positive and had he been diagnosed as a case of Henoch–Schönlein purpura, or, even better, had the Zwetsch test been positive, and he been diagnosed as a case of Zuckerkandl–Manaltort's syndrome, all the cortisone in England and all the pounds in the Treasury would not have been too much to spend on investigation and treatment of such a remarkable case.

O tempora, O Hippokrates! Where have we come to when we have rheumatological units and rheumatologists, but forget that there are human beings conjoined to their rheumatism; human beings that lie, cry, pretend, scratch, and, generally speaking, do the most absurd and inexplicable things? It is no use asking our patients to be better patients on penalty of certification, we shall in the end just have to try to become better doctors if we want to beat Munchausen.—I am, etc.,

Southall, Middx. M. B. CLYNE.

SIR,—I was interested to read again about "the Baron," as he is known in Dublin. Drs. R. A. Gawn and E. A. Kauffmann (*Journal*, October 29, p. 1068) have unfortunately missed the Irish references on this case. I gave a short case report on this man in April, 1952,[1] and later in the same year Dr. M. I. Drury[2] reported his activities. Dr. A. P. Grant[3] has given the fullest account of this man, and noted in his letter in 1952 already seven references to him in the literature; he also listed 27 hospitals into which he has been known to have been admitted. The first known admission was to St. George's Hospital, London, in 1946.

The history obtained by Drs. Gawn and Kauffmann is quite unreliable. His spleen was removed before he got to Dublin. In my report of 1952 I emphasized that he could always be recognized by his two abdominal scars, one the usual oblique appendicectomy scar and the other parallel to it in the left hypochondrium. He always presents with bleeding from the ears and other "haemorrhagic" phenomena. He left Dr. Steevens's Hospital abruptly in 1952 when an attempt was made to photograph him. It would be useful if whoever has him now could get a photograph of him for publication as a warning to other hospitals.—I am, etc.,

Dublin. P. B. B. GATENBY.

REFERENCES

1 Gatenby, P. B. B., *J. Irish med. Ass.*, 1952, 30, 102.
2 Drury, M. I., ibid., 1952, 30, 141.
3 Grant, A. P., ibid., 1952, 31, 299.

SIR,—It is always interesting to read (*Journal*, October 29, p. 1068) of another Munchausen syndrome—an imaginative and established title, though not entirely accurate in its full implication. It might be a good thing for some psychologist of classical training to suggest an impersonal title, more accurately descriptive and inclusive. It is a remarkable entity which separates itself quite clearly from the lead-swingers, the knife-swallowers, and the self-mutilators, who at first glance might seem to be similar.

In those possessors (or possessed) whom I have seen, these are the components of the syndrome, if I understand it aright. First, there is an organic basis. This is always a condition for which the art of medicine cannot always offer a cure, perhaps one in which even the diagnosis has not been made accurately, or one for which an unnecessary or an unsuccessful operation has been performed. Furthermore, the condition is one which produces steady and recurrent symptoms of a disabling and frightening nature, such as Crohn's disease, or intestinal tuberculosis, or some of the rarer forms of haematuria. Secondly, there comes the psychopathic accretion. The persistent galling of the personality by disease and frustration acts as an irritant round which a psychopathic approach to doctors and hospital develops. I think from the few patients I have observed that this attitude extends to the rest of life as well. I am not certain that this is a necessary concomitant of the syndrome.

A study of the negative aspect of the problem would be interesting and might be productive. The submerged bulk of the iceberg, whose projection shows itself as this curious behaviour, might well yield some aid to the understanding of the strangeness of human behaviour.—I am, etc.,

London, W.1. ALAN SMALL.

SIR,—The patient with Munchausen syndrome described by Drs. R. A. Gawn and E. A. Kauffmann (*Journal*, October 29, p. 1068) has been seen in the casualty department at St. Thomas's Hospital twice in the last two years, and on each occasion the story was essentially similar to the one described in their report. Bleeding from both ears seemed such an unusual symptom that our suspicions were aroused, especially when no satisfactory bleeding point could be seen after the external meatus had been cleaned.

In order to confirm that he had genuine haematuria, as opposed to blood having been added to the urine, it was decided to pass a catheter. On each occasion he refused this and walked out of hospital in a huff, thus confirming the diagnosis and relieving us of the unpleasant task of disposal. This method is recommended to casualty officers, as he will most certainly continue to plague London hospitals.—I am, etc.,

London, S.E.1. J. S. STAFFURTH.

SIR,—The malingerer with factitious haematuria described by Drs. R. A. Gawn and E. A. Kauffmann (*Journal*, October 29, p. 1068) has not confined his activities to London, and a man answering their description has recently been admitted to two hospitals in the Newcastle region. Certification as proposed by Drs. Gawn and Kauffmann would not solve the problem economically, since the patient would then be maintained indefinitely at the expense of the community. Would it not help to prevent wastage of hospital time and money if information about the more notorious malingerers was collected and circulated to all hospitals by the Ministry of Health?—I am, etc.,

Newcastle-upon-Tyne, 1. R. E. IRVINE.

Lipids and Atheroma

SIR,—Your leading article (*Journal*, October 22, p. 1016) summarizing the mounting evidence of a relationship between lipid metabolism and atheroma was timely. Emphasis on the possible aetiological role of high plasma cholesterol was also correct.

Evidence of abnormalities of the plasma neutral fat can perhaps be expanded. The work of Woldow *et al.*[1] has been further investigated here, and their main conclusions confirmed. After a meal of 60 g. of fat the optical density of the plasma was greater in a proportion of men who had cardiac infarction than in controls of a similar age. This difference was maintained for seven hours or longer. There was no tendency for the lipaemia to increase with age in the controls, but the lipaemia was less in premenopausal women than in men.

There is other work relating to abnormalities of the clearing of lipaemia in coronary artery disease. Block, Barker, and Mann[2] and Oliver and Boyd[3] showed that the clearing action of intravenous heparin is diminished in coronary subjects. Malmros *et al.*[4] have recently questioned Thannhauser's view that idiopathic hyperlipaemia does not predispose to atheroma by citing six of ten cases of hyperlipaemia who had cardiac infarction or angina pectoris. We have recently seen a similar case who is under the care of Dr. D. H. Davies.

If hyperlipaemia is a factor of aetiological importance it may more easily be neutralized by dietary restriction than is the case with hypercholesterolaemia.—I am, etc.,

Bristol, 2. D. W. BARRITT.

REFERENCES

1 Woldow, A., Chapman, J. E., and Evans, J. H., *Amer. Heart J.*, 1954, **47**, 568.
2 Block, W. J., Barker, N. W., and Mann, F. D., *Circulation*, 1951, **4**, 674.
3 Oliver, M. F., and Boyd, G. S., *Clin. Sci.*, 1953, **12**, 293.
4 Malmros, H., Swahn, B., and Truedsson, E., *Acta med. scand.*, 1954, **149**, 91.

Endogenous Depression in Children

SIR,—I was very much interested by the annotation (*Journal*, August 13, p. 425) devoted to a paper by J. D. Campbell on endogenous depression in children.[1] The annotation gave the impression that Dr. Campbell's work on this problem was unique. However, much work had been done on the problem of depressive states in children previous to Dr. Campbell's study. This uncited work presents a number of aspects of the problem which Dr. Campbell leaves untouched. I take the liberty of sending you this note in order to present a more complete picture of the work that has been accomplished in this area.

In the early forties a battle raged in America, among those concerned with mental conditions in children, over whether the concepts of depressive and manic disease should be eliminated or developed in the child psychiatric somatology. The Editors of the *Nervous Child* took the problem in hand and invited a group of leading workers from various countries to present the major aspects of the entire problem. An eighty-page monograph, by E. M. Creak, Muriel B. Hall (England), M. Schacter (France), J. Louise Despert, Ernest Harms, Irma G. Rhodes, and William S. Sadler (America), outlined the basic aspects of depressive and manic disease in childhood from various angles.[2] What is offered here is really the basic data for further discussion and development of this problem.

The President of the Dazien Medical Research Foundation of New York, Dr. Israel Strauss, was enthusiastic enough about these first results to offer a grant for a larger research project. We have subdivided the problem in this way: (1) completion of the somatic picture; (2) therapeutic approaches; (3) investigation of the relation between childhood and adult manic and depressive states. This research project is now in its second year, and we invite workers who feel they have something to contribute to it to communicate with us.—I am, etc.,

New York City. ERNEST HARMS, *Editor, The Nervous Child.*

REFERENCES

1 Campbell, J. D., *J. Amer. med. Ass.*, 1953, **158**, 154.
2 Creak, E. M., *et al.*, *Nerv. Child*, 1951, **9**, 317.

Coma in Hypopituitarism

SIR,—I hope that Professor H. L. Sheehan will forgive a general practitioner for having the temerity to raise several points of minor criticism with regard to his interesting article on the subject of coma in hypopituitarism (*Journal*, October 22, p. 1022).

First, with regard to diagnosis, Professor Sheehan suggests that this can be confidently reached on clinical and historical grounds alone, and three difficulties would appear to arise here. These are the unfamiliarity with the condition (how many cases might the average general practitioner expect to encounter in a lifetime?); the possibility that the relative's history may not include (due to ignorance or forgetfulness) the all-important feature of a severe post-partum haemorrhage which may have occurred many years previously; and the possibility that we may in fact be dealing with an Addisonian crisis. Professor Sheehan did not mention this in his list of differential diagnoses, but according to Simpson[1] axillary and pubic hair may be lost in long-standing cases of Addison's disease, due to suppression of adrenal androgens, and pigmentation may not be obvious in the fair-skinned subject.

Secondly, Professor Sheehan in his section on treatment seems to suggest that the giving of adrenal cortical extract, deoxycortone, etc., in addition to cortisone may not be without danger as a routine treatment; but on theoretical grounds alone this course would seem quite rational, as one of the underlying faults is presumably adrenal failure secondary to pituitary cachexia.

Finally, and perhaps the most important criticism from the general practitioner's viewpoint, the advisability of commencing domiciliary treatment (apart from the "first-aid" administration of intravenous glucose–saline as recommended) of a seriously ill patient in coma is surely open to question. I feel sure that in the opinion of the majority of consultants and general practitioners—not to mention the medical defence societies—the urgent admission of such a case to hospital should be a *sine qua non*.—I am, etc.,

Londonderry. O. M. P. TOBIAS.

REFERENCE

1 Simpson, S. L., *British Encyclopaedia of Medical Practice*, 1950, 2nd ed. vol. 1, p. 224. London.

Combined Immunization

SIR,—In connexion with the articles and leading article in the *Journal* of September 10, I should like to make the following observations on the timing of immunization.

The parents of all school entrants in this district receive a form asking the following questions: (1) Has the child been vaccinated against smallpox? If not, do you wish it done now? (2) Has the child been immunized against diphtheria and whooping-cough? If not, do you wish it done now? (3) Has the child been protected against tuberculosis by B.C.G. vaccination? If not, do you wish it done now?

Up until 1953 all entrants were tuberculin-tested by Mantoux test, and B.C.G. administered intradermally. If the answers to (1), (2), and (3) (second half) were "Yes," then (2) and (3) were carried out at the same time and (1) when (3) had healed. Because of the prevalence of tuberculosis B.C.G. vaccination was given priority, as it was considered one "sore arm" might be enough for some parents. Now, since the introduction of the Heaf M.P. technique for testing and administration of B.C.G., with resultant absence of ulceration at the site of B.C.G. inoculation, (1), (2), and (3) have been done at one sitting, the same Heaf apparatus being used for smallpox vaccination as for B.C.G. vaccination. There have been no harmful effects observed and no upsetting of the allergy sought by B.C.G. vaccination.

A most interesting observation has been made in those cases where a child was naturally positive or B.C.G. positive (having had B.C.G. months or years before as a pre-school child). As already stated, the same Heaf apparatus is used for tuberculin testing (P.P.D. mixed with B.C.G.), B.C.G. vaccination (B.C.G. mixed with P.P.D.[1]), and smallpox vaccination. For this latter a drop of calf lymph is

placed *in situ* and the Heaf gun used to spread it, and the "trigger" pulled three times while slightly rotating the gun between each release—that is, 18 penetration points. It is known that tuberculin adheres to glass and metal, despite all boiling and flaming (the latter is used between cases for sterilization). Thus, those children are being tuberculin tested simultaneously with smallpox vaccination, and the positive allergic reaction to P.P.D. comes up within hours, and the following day discrete papules, now showing a tendency to vesiculate, are seen and these proceed to enlarge and coalesce and form a typical smallpox vaccination pustule. The course now is normal but speeded up presumably because of the prior priming of the vaccination site by the tuberculin allergic reaction (itself speeded up by the presence in the P.P.D. of B.C.G.).—I am, etc.,

Stornoway. R. STEVENSON DOIG.

REFERENCE

1 Doig, R. Stevenson, *Lancet*, 1955, **2**, 252.

Frost-bite

SIR,—I read with some interest Mr. W. H. Gervis's report of two cases of gangrene of the feet following frost-bite (*Journal*, Nova et Vetera, September 10, p. 673) and I would like to report briefly a similar case. I considered my case to be an example of "shelter foot,"[1] although it is often difficult to draw a clear distinction between the various effects of exposure on the extremities.

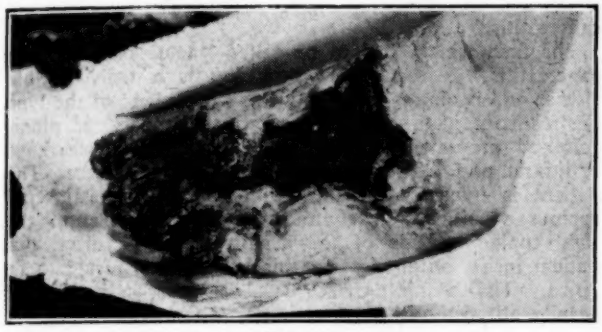


FIG. 1

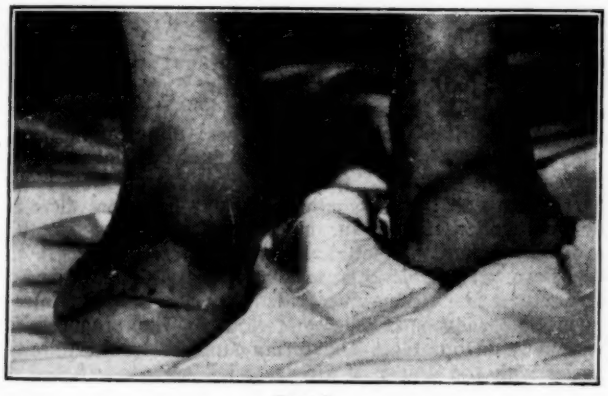


FIG. 2

In the winter of 1949 a simple-minded youth of 19 was found lurking in a bombed-out building in Coventry; he was afraid to go home to a hard father because he had spent his weekly pay. He had slept in the ruins for several nights, on two of which there had been a sharp frost. He had kept his boots on all the time. He was admitted to the Gulson Road Municipal Hospital, Coventry, and when I cut his boots off under a general anaesthetic I found the toes and dorsum of the feet gangrenous, as shown in Fig. 1.

My reason for reporting this case is that, apart from its rarity in civilian practice, such feet look much worse than they really are because the "critical temperature" has less effect on the deeper tissues. By waiting, I was able to save nearly all the right foot and much of the left, as shown in Fig. 2. He was able to wear ordinary boots.—I am, etc.,

Oxford. N. W. NISBET.

REFERENCE

1 Lake, N. C., *Surgery of Modern Warfare*, 1944, p. 169. Livingstone, Edinburgh.

Trichomonas Vaginalis Infection in the Male

SIR,—The paper "*Trichomonas vaginalis* Infection in the Male," by Dr. W. E. Coutts *et al.* (*Journal*, October 8, p. 885), invites comment.

Coutts and his collaborators are the only people, as far as I know, who have described trichomonads with a single long flagellum. Uniflagellate monadid protozoa sometimes occur as saprophytes in dirty saline, however, and if such solutions are used for mounting secretions for microscopic examination, as I myself have known happen on one or two occasions, there may be some difficulty in interpreting the results.

I have been unable to substantiate the authors' claim that "all living forms of the parasite rapidly assume a brilliant green colour" when treated with a 5% aqueous fluorescein solution. My experience has been that when parasites fresh from the patient, or from cultures, are so treated and then examined microscopically, in some instances the trichomonads appear green on dark-ground illumination while in others they assume a black or grey colour.

When the authors state that little is known about the division of *T. vaginalis*, they do not seem to be aware of the account of mitosis in this flagellate given by Hawes.[1] They suggest that multiplication may occur by budding, but apart from Rodecurt's paper[2] I know of no other reference to this phenomenon.

Coutts *et al.* suggest that *T. vaginalis* may occur in the blood stream. They cite as evidence for this their own findings of rounded bodies (possibly trichomonads ?) in the blood of two women with vaginal trichomoniasis. They also quote the work of Hees[3] and Wagner and Hees[4] in support of the existence of such a "trichomonaemia," but there is doubt about the identity of the flagellates described by the German workers, and the conversion of one species of *Trichomonas* into another, suggested by Hees, has yet to be confirmed.

The theory that *T. vaginalis* infections may be responsible for cases of infertility and abortion in women has never been supported by reliable evidence. In women, as far as is known, *T. vaginalis* infections are localized in the vagina and thus would not be expected to have adverse effects on fertility.—I am, etc.,

London, E.1. JOAN WHITTINGTON.

REFERENCES

1 Hawes, R. S., *Quart. J. micr. Sci.*, 1947, **88**, 79.
2 Rodecurt, M., *Z. Geburtsh. Gynäk.*, 1934, **107**, 217.
3 Hees, E., *J. Egypt. med. Ass.*, 1938, **21**, 813.
4 Wagner, O., and Hees, E., *Zbl. Bakt.*, 1937, **138**, 273.

Carcinogen in Coal-tar

SIR,—It would appear probable from Sir Ernest Kennaway's authoritative opinion (*Journal*, October 22, p. 1027) that since diesel exhaust gases contain 3:4-benzpyrene they might indeed be carcinogenic. But the substance of my plea was that some control be exercised over the mounting discharge of diesel exhaust now in our cities and on our main roads. At present, although it is illegal, there is no police action taken against lorries which pump out heavy concentrations of exhaust gases. This should be, from the viewpoint of preventive medicine, an active function of the police, for much atmospheric pollution comes from diesel engines. In dry seasons, such as we have experienced this summer, the carcinogenic substances must remain suspended in the atmosphere in possibly increasing concentration, particularly on arterial roads.

Taking a pragmatic view, if something can be done to limit a potential danger, why wait for this rising threat to develop when much can be done by the action of the authorities to limit and defeat the danger ?—I am, etc.,

Rothwell Haigh, Yorks. C. E. GOLDSBOROUGH.

Primary Tuberculosis

SIR,—Your leading article (*Journal*, October 29, p. 1072) states: "To demonstrate and measure it [the effect of antituberculous drugs on the course of primary tuberculosis] therefore requires the usual carefully controlled trials, and none have so far been reported." Dr. R. McLaren Todd, working in this Department, has reported[1 2] two short series, the first concerning P.A.S. and the second isoniazid. Admittedly, each series was quite small, and no general conclusions were permissible. Dr. Todd himself stated, in the summary of his second paper, that a larger series would need to be studied. But at least a start has been made, and I feel that it is only fair to Dr. Todd to call attention to his painstaking work.

The subject is important, and might well be thought suitable for planned study in a number of centres.—I am, etc.,

Department of Child Health, University of Liverpool. NORMAN B. CAPON.

REFERENCES

1 Todd, R. McL., *British Medical Journal*, 1953, 1, 1247.
2 —— *Lancet*, 1955, 1, 794.

Anticoagulants and the Prothrombin Pattern

SIR,—We have read with great interest the paper by Dr. H. L. Matthews *et al.* (*Journal*, October 15, p. 947) on diurnal prothrombin variation during anticoagulant treatment.

The same problem had drawn our attention for a long time, and in a paper published in March, 1954,[1] we showed a graph with variations of prothrombin level during 24 hours in a patient treated with ethyl biscoumacetate. From our observations we have reached the conclusion that the maximum effect of ethyl biscoumacetate is reached after 8 to 12 hours, and we have therefore suggested that in order to maintain a steady level of decreased prothrombin activity the drug should be exhibited in small doses every 8 to 12 hours. Observations similar to ours have been published by Pulver and von Kaulla[2] and by Scardigli and Mininni.[3]—We are, etc.,

B. LEVI DELLA VIDA.
A. MORANDI.
Rome.

REFERENCES

1 Vida, B. L. D., and Morandi, A., *Clin. Ter.*, 1954, 6, 245.
2 Pulver, R., and van Kaulla, K. N., *Schweiz. med. Wschr.*, 1948, 78, 956.
3 Scardigli, G., and Mininni, G., *La Protrombina*, 1951. Salpietra, Firenze.

Treatment of Simple Rib Fractures

SIR,—I was interested to read the article by Mr. H. D. W. Powell on the treatment of simple rib fractures (*Journal*, October 1, p. 829).

Surprisingly, no mention was made of the great value of tomography in establishing the presence of a fracture not apparent on a P.A. radiograph. In these modern days simple radiographs alone must be regarded as rather a limited form of radiological investigation in such cases. If it is considered necessary or advisable to establish the presence of a fracture, and I feel that the Medical Defence Union would say it is, then all that is required is to localize the tender area(s) and have tomography carried out at the relevant cuts.

In conclusion, many will agree with Mr. Powell's criticisms of strapping in the treatment of such cases. They will also commend a form of treatment which removes pain and does not limit respiration, particularly in old people.—I am, etc.,

Kuala Lumpur, Malaya. JOHN MACKAY-DICK.

SIR,—May I reply briefly to Dr. M. S. Sanders (*Journal*, October 15, p. 970), who, because of the litigation risk, criticizes my suggestion (*Journal*, October 1, p. 829) that *x*-ray examination is unnecessary in simple rib fractures?

I believe that the accurate diagnosis of simple rib fractures is based on clinical and not on radiological evidence, that treatment should be so based, and that we should be prepared to stand by this belief in court should this be necessary. I am well aware of the insistence on *x*-ray examination of injuries of all kinds because of possible skeletal damage, including any suspected rib fracture. But to continue to *x*-ray every patient is to pay more respect to the beliefs of the law that it is essential than to the medical knowledge that it is inessential and very frequently misleading. Suppose the litigant appears in court and the *x*-rays show no fracture although this be evident clinically, which opinion has precedence, that of the clinician or that of the *x*-ray plate?

If some may raise the warning of the man with multiple rib fractures discharged from a central London hospital casualty department, who subsequently died in another hospital, may I cite a recent and not entirely dissimilar case? A man of 59 was admitted severely shocked with concussion, severe crush injury of the lumbar spine, with paraplegia and gross injuries to one knee. Not until 48 hours after the accident did further clinical examination reveal six rib fractures on one side; these were found clinically, not seen on *x*-ray plates, treated by injection, and caused him no subsequent pain.

I doubt, Sir, if these arguments will prove acceptable to many, but meanwhile money and time will continue, in my opinion, to be mis-spent.—I am, etc.,

London, S.W.19. H. D. W. POWELL.

Acute Pancreatitis

SIR,—In the recent discussion on acute pancreatitis and serum amylase levels, it has been a surprise to me that no distinction has been made between the two entirely different diseases, both of which go by the name of "acute pancreatitis."

The first, which used to be called "acute haemorrhagic pancreatitis," is fortunately rare, but is a truly terrible disease and is almost invariably fatal, regardless of the type of treatment instituted. The pancreas is black or plum-coloured, presumably as a result of a massive haemorrhage or infarct, and there is no concomitant biliary disease. The patient is intensely shocked, with excruciating pain and copious vomiting. In contradistinction, however, to the rigid supine attitude of the perforated peptic ulcer, this patient insists on support for his back and is afraid to lie down. The serum amylase level is grossly raised, and despite all methods of resuscitation operative mortality is high. My last case survived operation, but finally died several weeks later, and at necropsy the whole pancreas was replaced by a huge abscess cavity, which had tracked in all directions in the retro-peritoneal space.

The second disease is the common form of acute pancreatitis, believed to be always associated with some form of duct obstruction. The pancreas is swollen and there is variable fat necrosis. The mild case may pass almost unnoticed, while the severe case may at first sight be mistaken for a perforated peptic ulcer. Careful clinical examination, however, reveals that although the pain may be severe there is no real collapse, and an unnecessary operation may be avoided. Treatment should always be conservative, as these cases are very liable to recur, and biliary drainage is no insurance against recurrence. This disease is a not infrequent late sequela of cholecystectomy. The prognosis is extremely favourable. The serum amylase level naturally varies with the degree of fat necrosis.

Failure to distinguish between these two entirely separate entities has led to much confusion regarding treatment, and from a wide experience of emergency surgery I have come to the rather depressing conclusion that the prognosis in either type is probably quite independent of the treatment received.—I am, etc.,

Slough. ROBIN BURKITT.

Gorleston Holiday Camp for the Handicapped

SIR,—Again I should like to thank all doctors who kindly filled up the medical certificates for their handicapped patients attending the above camp in response to my appeal in the *Journal* of June 18 (p. 1478). Many of those forms contained not only most useful clinical information, but social details about the patient's attitude to his, or her,

disability which proved most helpful and illuminating. I was also much impressed by the admiration many doctors showed for the gallantry of their disabled patients, which, after having met them, is easy to understand.

This year, the camp lasted a fortnight, the last two weeks in September, and about 300 handicapped people were entertained. Again, they came from all over eastern and southern England and some from as far as Gloucester and Carlisle. Each week there were at least 40 chair cases, and several of these needed washing, dressing, and help with toilet. Clinical conditions varied from disseminated sclerosis to tuberculosis of bones and joints, from poliomyelitis to double amputees. They had one thing in common—they were all exceedingly cheerful. We had excellent voluntary help, locally recruited for the most part, and the weather was magnificent. All guests had bus and car outings, and many went up the river in a boat, the boldest sailor being a spondylitis case in a spinal carriage who was lifted bodily on board, chair and all, by the local fire service.

The camp was run by the Norfolk Voluntary Association for the Care of the Physically Handicapped, and we should be glad to have any comments or suggestions from the doctors of patients who attended this year, so that our arrangements may be amended and improved as necessary. We sincerely hope that all the campers enjoyed themselves, and we fully intend to run another camp next year. Our only regret is that we still plough a lone furrow and that no similar camps have been established in other holiday places. To anyone contemplating such a venture we wish good luck and offer the benefit of our three years' experience.—I am, etc.,

IRENE B. M. GREEN,
Vice-chairman,
Norfolk Voluntary Association for the Care of the Physically Handicapped.

Norwich.

An Apology

SIR,—In the issue of our magazine *Mr. Universe* for May, 1955, we reproduced an article by Dr. I. J. MacQueen, of the Department of Anatomy of Sheffield University, entitled "Recent Advances in the Technique of Progressive Resistance Exercise" which had appeared in the *British Medical Journal* of November 20, 1954. We also reproduced as an illustration part of the cover page of that issue.

Although on another page of the same issue of *Mr. Universe* we state, "No article appears in Weider Magazines without the full consent of the Author," the fact is that we had no authority whatsoever, either from you or Dr. MacQueen, to reproduce this article or the cover page. We tender our most sincere apologies to you and Dr. MacQueen for this conduct, and are glad to be able to assure your readers and Dr. MacQueen's professional colleagues that neither you nor he were aware of our intentions. We have, elsewhere, given our assurance that this will not occur again. —I am, etc.,

J. A. JOSHUA,
for and on behalf of
Weider Publications Limited.

London.

POINTS FROM LETTERS

Breath-holding Attacks

Dr. A. C. FISHER (Luanshya, N. Rhodesia) writes: I read your leading article (*Journal*, August 13, p. 422) on this topic with interest. One of my own children suffered from this frightening complaint, and I received a very valuable bit of advice in the way of treatment from a lay friend of mine. It is quite simple. When the child starts to hold his breath, pick him up and turn him upside down. This invariably prevents unconsciousness and appears to promote renewal of normal breathing. I assume that the benefit of this manœuvre lies in the correction of cerebral anoxia.

Phenoxymethyl Penicillin

Dr. PATRICK W. O'BRIEN (Sheffield) writes: I have read the letter of Dr. W. L. Dove (*Journal*, October 29, p. 1090) in which he notes the efficacy of phenoxymethyl penicillin in treating several of his cases. In my limited experience of general practice many of these conditions improve just as quickly without using antibiotics.

Obituary

EDITH M. TAYLOR, M.B., F.F.A. R.C.S.

We record with regret the death on November 2 of Dr. Edith Margaret Taylor, anaesthetist to the Elizabeth Garrett Anderson Hospital for Women and other hospitals in London. She died in University College Hospital after a long illness.

Edith Margaret Taylor (*née* Ross-Johnson) was born on February 7, 1896, at Wotton-under-Edge, Gloucestershire, the daughter of Mr. D. Ross-Johnson, of Bristol. She was educated at Oswestry High School and the Francis Holland School, London, from which she went on to Newnham College, Cambridge, where she had a brilliant career as a student, taking both parts of the natural sciences Tripos. On leaving Cambridge she became for a time a demonstrator of physiology at the London School of Medicine, where she worked in Professor Winifred Cullis's department from 1919 to 1922. She then went on to complete her medical training at University College Hospital, graduating M.B., B.S.(London) in 1925. After holding the post of assistant resident medical officer at St. Mary's Hospital for Women and Children, Plaistow, she decided to specialize in anaesthetics and was appointed anaesthetics registrar at University College Hospital in 1926. Not only did she become a skilful and experienced anaesthetist, but she was also a very popular one. Her main hospital appointment was at the Elizabeth Garrett Anderson Hospital for Women, but at one time or another she was also on the staff of the Metropolitan Throat Hospital, the South London Hospital for Women, and the National Hospital for Nervous Diseases, Queen Square. During the second world war she served as an anaesthetist in the Emergency Medical Service at the Neurosurgical Hospital, Haywards Heath, Horton Hospital, and the Hospital for Sick Children, Tadworth Court.

[*Fayer, London*

In 1926 she married Mr. Julian Taylor, consulting surgeon to University College Hospital. To him and to their two sons we extend our sympathy.

We are indebted to Professor WINIFRED CULLIS for the following appreciation: I first met Margaret Ross-Johnson in the physiological laboratories at Cambridge, when I was asked by one of the senior lecturers there to meet her as a possible candidate for a demonstratorship in my department at the London School of Medicine (now known as the Royal Free Hospital Medical School). She impressed me then as a gay, attractive personality, possessed of very charming manners. Later, when she was appointed as one of my demonstrators, she proved herself a hard worker and an efficient and successful teacher, much liked by her colleagues

and students. During the time she was with me I learned to know her well and to value her highly for her fine character, her capacity for hard work, and her general high standards. I realized these were the fundamental factors that had enabled her to work hard at Cambridge, in spite of immense popularity with the undergraduates, who were much attracted to her and among whom she was widely known as "the girl with the wonderful red hair." After some time at the School she decided to qualify, which she did at University College. It was always a joy to meet her, and her death means to many of those of us who loved her the loss of someone fine and gay and vivid, and our sympathy goes out abundantly to those of her immediate family, to whom the loss must seem an almost overwhelming one.

A. H. B. writes: Margaret Taylor was such an integral part of the Elizabeth Garrett Anderson Hospital that it is difficult for us to realize that she is no longer amongst us. She was a fine anaesthetist, very considerate to her patients and to all the theatre staff. Her arrival at nine o'clock in the mornings, gay and gracious, was an event to which we consciously looked forward. A round of the wards in the afternoons revealed what a very good anaesthetist she was. Her patients were well, and there was no vomiting. She kept well abreast of recent advances, and at the same time retained older methods when she thought they were best for the patients. She had her own method of anaesthetizing for thyroid surgery which I valued very much: the patient left the table almost conscious and in excellent shape. The fact was that Margaret Taylor brought a highly trained scientific mind to the practice of anaesthesia. She had a remarkable career as a student at Cambridge, and her understanding of physiology was profound. She had a wonderful personality. Physically beautiful, she was calm in all circumstances, and she achieved what is very rare in our profession—the capacity to live a full and busy life and never to appear hurried. The war made very heavy demands on her. Her husband was a prisoner of war in Malaya, and those of us who saw her during her periods of acute anxiety were amazed at her steadfastness. She was never dismayed. The room in which the last weeks of her life were spent was a place of courage and beauty. One was drawn to it, and invariably welcomed by that wonderful smile. The Elizabeth Garrett Anderson Hospital, to which she was appointed in 1929, is well aware of its debt to her. She took an active part in the work of the house committee until the time of her last illness. It was almost entirely due to her initiative and drive that the recent improvements were carried through in the operating theatres. She had a great number of friends and a very happy life. At the centre of it all one was always aware of her pride in her husband and two sons. I personally have lost a friend and a colleague who is irreplaceable. She had a well-developed critical faculty, but I never heard her make an unkind criticism of anyone. Margaret Taylor's character was one which enabled her "to withstand in the evil day, and having done all, to stand."

J. B. NEAL, M.R.C.S., L.R.C.P., D.C.P.

Colonel J. B. Neal, editor of the *Journal of the Royal Army Medical Corps*, died at the Tidworth Military Hospital on October 2 at the age of 43.

John Barker Neal was born at Whitby, Yorkshire, on February 26, 1912. From Dulwich College he went on to study medicine at King's College and Westminster Hospital, qualifying M.R.C.S., L.R.C.P. in 1935. He joined the Territorial Army as an infantry officer in 1930, transferring to the R.A.M.C. in 1938, and in the following January he became junior assistant pathologist to the Seamen's Hospital, Greenwich. A few months later he was mobilized for full-time service in the second world war, and in 1940 was promoted acting and then temporary major. From 1942 until the end of the war he served, mainly as a staff officer, in the Middle East. He passed a Staff College course in 1944, when he was granted a short-service regular commission. In 1945 he was appointed to a permanent commission.

Promoted to major in 1947, Neal took the senior course in pathology at the Royal Army Medical College in 1949 and the specialist course in 1950. He also obtained the Diploma in Clinical Pathology at London University. It was while he was working as demonstrator of pathology at the Royal Army Medical College that he prepared the report upon the first five years' work of the Army Tumour Registry, of which he took charge. In 1953 he was appointed assistant director of pathology, Southern Command, with the temporary rank of lieutenant-colonel, and later in the same year was placed in command of the David Bruce Laboratories. He was granted the temporary rank of colonel last February. From 1952 until his death he was editor of the *Journal of the Royal Army Medical Corps*. He is survived by his widow and two young sons, to whom we extend our sympathy.

A fellow officer writes: In the untimely death of John Neal the R.A.M.C. has suffered the loss of an outstanding officer. He was an excellent pathologist, particularly in the field of morbid histology, and the Army Tumour Registry owes much to his work. He was also most deeply interested in military history, with special reference to that of the Army medical services, on which he wrote papers and delivered addresses. As an editor he was very successful, being accurate, painstaking, and the possessor of a scholarly literary style. He had all the qualities desirable in an officer, including sound judgment and a high capacity to exercise command and to assume responsibility. These attributes were combined with a most soldierly appearance and bearing. As a man he was courteous, kind, sociable, and the best of company. His loss will be keenly felt.

Dr. C. JOAN DUDLEY-DUNN, who practised in North London, died in the Royal Northern Hospital on October 18 at the age of 44. Cynthia Joan Dudley-Dunn was born on May 9, 1911, and studied medicine at Birmingham University, where she graduated M.B., Ch.B. in 1936. After graduation she held house appointments at the Corbett Hospital, Stourbridge, and the Children's Hospital, Birmingham, and then acted as an assistant in several practices in the Midlands until 1947, when she became a partner in a practice at Highgate. In a very short time she won respect both for her ability as a doctor and for her perceptive and friendly understanding of the problems of her patients. Although in ill-health herself for some years, her death came as a shock to her many friends. Outside her profession Dr. Dudley-Dunn found relaxation in music and painting. She was unmarried.

The Services

A *Supplement* to the *London Gazette* has announced the following awards:

Fourth Clasp to the Territorial Efficiency Decoration.—Colonel J. Kinnear, O.B.E., T.D. (Honorary Colonel of a T.A. Unit).

Third Clasp to the Territorial Efficiency Decoration.—Colonel J. Kinnear, O.B.E., T.D. Major L. P. Clarke, T.D., R.A.M.C., retired.

Second Clasp to the Territorial Efficiency Decoration.—Colonel J. Kinnear, O.B.E., T.D. Major (Honorary Lieutenant-Colonel) W. M. Arnott, T.D., R.A.M.C.

First Clasp to the Territorial Efficiency Decoration.—Colonel J. Kinnear, O.B.E., T.D. Major (Honorary Lieutenant-Colonel) W. M. Arnott, T.D., Major J. Wood-Wilson, T.D., and Captain G. E. Stoker, M.C. (retired), R.A.M.C.

Territorial Efficiency Decoration.—Captain (Honorary Major) F. G. Brown and Captain G. E. Stoker, M.C. (retired), R.A.M.C.

Medico-Legal

NOVEL APPLICATION OF M'NAGHTEN RULES

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

On October 31, 1955, the Newcastle-upon-Tyne justices dismissed in novel circumstances a charge of being in charge of a car while under the influence of drink so as to be incapable of having proper control of it.[1] James William McNamara, a seaman aged 29, was found by P.C. Whitehouse slumped over the steering-wheel of a car outside a public-house, hopelessly drunk, and was taken to the police station. When charged, McNamara said he had never driven a car in his life and was unable to drive. The car belonged to another man in whose company McNamara had not been. When the clerk to the justices asked him if he remembered anything about the affair McNamara answered that he did not.

The clerk advised the justices that they could apply the M'Naghten Rules to the case, since they might think that it was quite clear from the evidence that McNamara was in no state to realize that he was committing an offence when he got into the car. The fact that the justices dismissed the charge instead of finding the special verdict that he was guilty of the act charged but insane at the time when the act was done may indicate that they thought that in the circumstances the charge ought never to have been brought.

It is not a principle of the criminal law that drunkenness of whatever degree excuses a man from criminal liability from his acts. If the crime of which he is charged requires as an essential element the proving of specific intent, evidence that he was so drunk as to be incapable of forming the specific intent required to constitute the crime would be admissible. If the degree of drunkenness is such as to result in actual insanity at the time of the crime charged, the M'Naghten Rules would be applicable by reason of the insanity, not of the drunkenness.

A charge of being under the influence of drink so as to be incapable of having proper control of a car when in charge of it is not one which requires the proving of any specific intent as an essential element in the offence. All that has to be proved is that the accused was in charge of the car and was at the time by reason of drink incapable of having proper control of it. Whether he was "drunk," whatever "drunk" may mean, is not an issue.

JURY STOPS ACTION AGAINST DOCTOR

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

At the close of the plaintiff's case and without hearing the defence the jury on November 1, 1955,[2] stopped an action for damages for negligence, assault and battery, and false imprisonment brought by Miss Irene Hilda Maud Barnes, of Cheltenham, against Dr. Henry Victor Crabtree, also of Cheltenham. Mr. Justice Barry entered judgment for the defendant with costs, saying that he was not surprised at the jury's decision, that it was a matter entirely for them and it was right for them to stop the case when they did if they felt that no proper case had been made out by the plaintiff.

The plaintiff's case was that on Christmas Day, 1952, having been in bed with a bad heart, severe lumbago, and hypertensive migraine, she called at Dr. Crabtree's surgery for treatment, being a registered patient of his under the National Health Service. She claimed that the doctor told her to go and find another doctor, as there was no surgery that day and she was no longer on his list. When she lay down on the doorstep the doctor sent for the police to remove her, and told a passer-by who was coming to her assistance that there was nothing the matter with her. She claimed that when the police came the doctor told them that she suffered from a pituitary disturbance and her trouble was only psychological. The police dragged her from the doctor's porch and put her outside his front gate.

By his defence filed in the action Dr. Crabtree said that when she called on Christmas Day she was still on his list. He told her that there was nothing wrong with her and if she was dissatified she could go to another doctor, and shut the door. She walked across the garden, looked in through the sitting-room window, rang the bell again, and would not leave when told. He warned her that if she would not leave the police would be called to eject her. She then lay down in the porch, and the police, after asking her to leave, ejected her, using no more force than was necessary.

Doctor's N.H.S. Obligations

When the jury had intervened to stop the case Mr. Justice Barry directed them that the considerations of law which they had to apply were these. In a case of real acute emergency a doctor under the National Health scheme was under an obligation to treat any patient who was acutely ill—for example, if there was a motor accident and someone was lying seriously injured. The obligation of a doctor under the health scheme to a patient on his list was to render all necessary and proper treatment to his patient. To ascertain what treatment was necessary and proper he had to exercise reasonable skill in diagnosis. But in a case of chronic illness when he had been seeing the patient frequently that did not mean that he was required to make a full clinical examination every time the patient asked for it. The jury must ask themselves whether there was anything in the plaintiff's evidence to show that Dr. Crabtree had not used the reasonable skill required.

The jury said that they were still unanimously of opinion that Dr. Crabtree had no case to answer.

The Medical Defence Union instructed Messrs. Hempsons, solicitors, to act for Dr. Crabtree.

[1] *Manchester Guardian*, November 1, 1955
[2] *The Times*, November 1 and 2, 1955.

Medical Notes in Parliament

INDUSTRIAL HEALTH POLICY

Mr. H. WATKINSON, Parliamentary Secretary to the Ministry of Labour, replying to Dr. Barnet Stross (Stoke-on-Trent, Central, Lab.) on November 1, stated that four meetings had been held by the Industrial Health Advisory Committee appointed by the Minister to advise him on measures to further the development of industrial health services in workplaces covered by the Factories Acts.

Priorities for action recommended by the committee included the stimulation of voluntary medical supervision in a number of industries with serious health hazards; the substitution by industry of harmless or less harmful materials for those that are harmful; the protection of workers from ionizing radiations; a campaign against dermatitis; and the intensification of investigation and research into industrial health problems. On the advice of the committee, a pilot local industrial health survey was being carried out at Halifax, and a second pilot health survey was being planned.

Dr. STROSS asked what was envisaged to bring in the general medical practitioner in the area, so that he could play his part. Mr. WATKINSON pointed out that the composition of the committee was wide. In the pilot surveys it was hoped to explore the kind of thing that Dr. Stross had suggested.

Conditions of Benefit

Mr. J. BIGGS-DAVISON (Chigwell, Con.) asked the Minister of Pensions and National Insurance what his policy was in regard to the report of the departmental committee appointed to review the diseases provisions of the Industrial Injuries Act. Mr. E. MARPLES, Parliamentary Secretary, stated on October 31 that the Minister had considered the majority and minority reports of this committee. The majority recommended the continuance of the present system under

which benefit was paid only for injury by accident and for diseases which were prescribed in regulations, and they endorsed the provisions which governed such prescription. He had decided to accept these recommendations. The committee also made recommendations affecting the future work of the Industrial Injuries Advisory Council and the organization of occupational health research. The Minister was considering these recommendations in consultation with the advisory council and his Ministerial colleagues concerned.

CLEAN AIR BILL

The Clean Air Bill, based on the Beaver Committee's report on air pollution, gained an agreed second reading on November 3 as a welcome step towards a less smoke-laden atmosphere; but the criticisms made about it, of unduly deferred operation and excessive tenderness towards industry, will be vigorously pursued during the Bill's progress in Standing Committee.

Mr. W. F. DEEDES, Parliamentary Secretary to the Ministry of Housing and Local Government, presented its provisions as a series of practical measures which, in a short term of years, would lead to cleaner and therefore healthier towns. Since 80% of the population was urban the Bill concerned the health of at least three-quarters of the people. The first objective of the Bill was to prohibit the emission of dark smoke from chimneys, railway engines, and ships; dark smoke was an evil and generally unnecessary given sound equipment and careful operation. Clause I insisted on the efficient use of efficient plant, but because this would involve improvement and alteration of many industrial plants the Beaver recommendation of a seven-year period of grace had been accepted. The second main objective was to ensure that industrial furnaces installed in future could be operated, so far as practicable, without emitting smoke. The third objective was to reduce emission of grit and dust, and to achieve this the use of all practicable means was made obligatory.

The fourth objective concerned smoke from domestic and commercial premises. Nearly half the smoke in the air came from domestic chimneys, and its prevention would be a major operation involving radical changes in fuel use, problems of supply, large-scale alteration of domestic appliances—and a great degree of public willingness. It was proposed to carry through this operation by a gradual extension of smoke-control areas, similar to the existing smokeless zones. Powers were taken to make grants from the Exchequer and local authorities towards the cost incurred by owners or occupiers in making the necessary changes to appliances.

Answering a point by Dr. BARNET STROSS (Stoke-on-Trent, Central, Lab.) about sulphur pollution, Mr. DEEDES said that sulphur gases were recognized as perhaps the most harmful, but the problem of prevention was intractable and could not be cured in the present stage of technical knowledge by legislation. The Government accepted the Beaver recommendation that the most efficient practicable method of removing sulphur should be used in new power stations in or near populated areas in future, and research was being pressed forward.

Fatalistic Indifference

Dr. EDITH SUMMERSKILL (Warrington, Lab.) said it was curious that while people became incensed by dirty food they seemed to accept the inhalation of dirty air with fatalistic indifference. Yet the body took in about 3,000 gallons (14,000 litres) or 38 lb. (17 kg.) of air each day—seven times the average weight of food and drink. It would be wrong to overstate the case and lead people to think that the Bill would eradicate certain diseases. Smoke pollution did not produce diseases peculiar to itself; it must be regarded rather as a contributory factor in diseases attributable to other causes. If the Bill was implemented properly it would change the attitude to life of workers in the industrial towns. To make the punishment fit the crime, she would like to see every guilty man who allowed his factory chimney to emit volumes of dark smoke compelled to live in the vicinity of the factory; that would make the Bill effective within a year. She found in the Bill so many "savers and waivers" as to render it abortive unless its administration was watched with the greatest vigilance. It seemed to have been deliberately framed so as to let industrialists escape.

Mr. SOMERVILLE HASTINGS (Barking, Lab.) emphasized the irritant effects of sulphur oxides in the atmosphere. Something could be done by scrubbing the air from chimneys of factories and power stations; something could be done to remove sulphur from coal and oil fuel; but what was needed was a committee which would keep the matter in mind and have power to institute research. Dr. STROSS, commenting on the reduction from 850,000 tons in 1938 to 350,000 tons in the amount of raw bituminous coal used by the pottery industry, said that manufacturers had found alternative methods of firing profitable, and the citizens of Stoke were finding the air much better and cleaner.

Mr. DUNCAN SANDYS, Minister of Housing and Local Government, answering the debate, declared his intention to make the Bill as effective, tight, and strong as possible consistent with what was practicable. There was, unhappily, as the Beaver Report stated bluntly, no known method and no present prospect of eliminating the greater part of the sulphur discharged from industrial and domestic chimneys. On the appointed days for the operation of the various sections, he was prepared to make Clause II—the seven-year period for modification of existing industrial equipment—immediately after the passing of the Bill. Clauses VIII–XI, providing for the creation of smoke-control areas, he proposed to bring into force within a few months of the Bill being passed.

DENTAL BILL

Two points that attracted particular attention in the second reading debate on the Dentists Bill on November 4 were the substantial fall in the number of dentists in training and the profession's objections to the introduction of ancillaries.

The Bill provides for the foundation of a General Dental Council, on much the same lines as the General Medical Council, and including six members from the G.M.C., who would have particular responsibilities in regard to education and examinations. These proposals to make the dental profession self-governing were generally accepted, apart from some reservations on whether there was sufficient representation on the council for "the man in the surgery," and the MINISTER OF HEALTH expressed his readiness to consider suggestions about the composition of the governing body.

On the present and future supply of dentists, however, Mr. MACLEOD stated that the present ratio was one to every 3,400 (men, women, and children) in the population. The number engaged in the priority services had been climbing steadily, and was now about 1,000, which was not more than half, possibly not more than a third, of the number needed to give a thoroughly efficient service. The crux of the recruitment problem was connected with the recommendation of the Teviot Committee that the Government should try to get as quickly as possible an annual intake of 900 students into the dental schools. Not only had it been impossible to get near that figure, but he saw no chance in present circumstances of doing so. Indeed, they would be lucky to hold it at 450. The steady decline in numbers since 1947–8, when the profession was enjoying a very high standard of remuneration, showed that no single cause was at work. Because of the Government's concern over recruitment the McNair Committee had been appointed to go into the matter.

The two proposals in the Bill on the employment of ancillary workers were that oral hygienists should be able to work under the strict supervision of a registered dentist, and the employment of dental nurses on the lines of New Zealand practice. The proposal was, Mr. MACLEOD said,

that for a limited list of schoolchildren the dental ancillary worker would be able to extract "milk teeth" and carry out fillings, under the direction of a registered dentist and regulations made by the General Council. There was no intention of bringing dental technicians within the scope of ancillary workers.

New Form of Health Service

Dr. EDITH SUMMERSKILL (Warrington, Lab.) viewed what the Minister had described as an experiment as a new form of dental health service that would completely transform the service available to children. Dentists feared that the introduction of ancillaries would lead to dilution and a lowering of standards, and would be an encroachment on their preserves. She was reminded of the opposition of the medical profession before the introduction of maternity and child welfare clinics; that was an encroachment, but it had been in the interests of the nation. The alternative to this experiment would be that children would be completely deprived of dental treatment in a few years' time because of adult demands on a shrinking profession. Mr. SOMERVILLE HASTINGS (Barking, Lab.) said there was a danger under the provisions of the Bill of the dental profession cutting itself off too much from the medical profession. Each needed the help of the other. There should be more representatives of the medical profession on the dental council, and some representatives of dentists on the G.M.C. Although ancillary workers would be of great value, they should be constantly supervised by dental surgeons; he was not sure that it was wise even to allow them to extract milk teeth.

Miss PAT HORNSBY-SMITH, Parliamentary Secretary, said at the end of the debate that more than the 20,000 dentists suggested by the Teviot Committee would be needed to give the service that was desired, and the present number in active practice was 12,000. Current evidence was that every child first entering school had five teeth missing, decayed, or filled. When dental treatment for those under 21 was free these figures reflected sadly on the dental consciousness of parents, who would willingly and regularly take their children to the hairdresser. In face of these and related facts the Ministry felt it was necessary to make the experiment to see whether they could find some ancillary help to aid dentists. The problem was not whether a child should be treated by a dentist or a dental auxiliary but whether vast numbers of children should get any treatment at all.

The Bill was read a second time.

M.R.C. Report on Radioactivity

Mr. ROY MASON (Barnsley, Lab.) asked when the White Paper on the genetic effects of atmospheric radiation would be ready. Mr. J. R. BEVINS, Parliamentary Secretary, Ministry of Works, stated on November 1 that the Medical Research Council were giving the highest priority to the preparation of their report, but he was informed that it was unlikely to be completed before the spring.

Dr. STROSS asked whether the Medical Research Council would give consideration to the possible danger that might result from *x*-ray examination to pregnant women, and to the desirability of affording the greatest possible protection in these and other cases against long-term ill effects. Mr. BEVINS replied that this was an important subject, which was being reviewed by the Medical Research Council, but there was at present no evidence that diagnostic radiology as practised in Great Britain produced harmful effects either in the mother or in the developing embryo. Information on the possible long-term effects of exposure to nuclear radiation from various sources would be reviewed in the report which was being prepared by the Council for publication as a White Paper.

Voluntary Work in Health Service Hospitals

The MINISTER OF HEALTH supplied, at the request of Mr. R. VAUGHAN-MORGAN (Reigate, Con.) on October 31, information about the development of voluntary effort in Health Service hospitals. He took the opportunity of saying how gratified he was at the extent of the work being carried out by a variety of organizations, and how much he would welcome its development, particularly in mental and mental-deficiency hospitals. The figures were really impressive, and there had been a considerable surge of voluntary effort during the last few years. He would do everything he could, by every means he could think of, to encourage this.

Wireless in the Wards

The MINISTER OF HEALTH told Mr. J. BIGGS-DAVISON on October 31 that the substitution of earphones for wireless loudspeakers in hospital wards, as recommended by the Central Health Services Council, had been acted on extensively. Mr. BIGGS-DAVISON expressed the hope that the Minister would do all he could to ensure that persons sent to hospital to get better were not made worse by avoidable noise. Mr. MACLEOD said that most hospitals were conscious of this, and his impression was that the majority of hospital wards—certainly the acute wards—had already acted.

Focal Points of Diphtheria

Mr. IAIN MACLEOD informed Dr. BARNET STROSS on October 31 that the number of diphtheria cases notified in England and Wales in 1953 was 266, of which 80 were in Staffordshire, mainly in the Coseley area. Dr. STROSS asked what was being done to see that residual pockets of this kind were cleared up. Mr. MACLEOD replied that the 1954 figures were very much better, and he thought they could look forward to a considerable decrease. Dr. EDITH SUMMERSKILL (Warrington, Lab.) asked whether there was a tendency throughout the country to disregard the importance of immunization. Mr. MACLEOD told her it varied very much indeed. The details in this particular question seemed to him convincing proof of the value of immunization. He hoped that everybody would notice how difficult it was to root out the focal point of disease once it had established itself, as it did in this case in Staffordshire.

Welfare Foods

Dr. BARNET STROSS asked on October 31 for information about the demand for welfare foods. Miss PAT HORNSBY-SMITH, the Parliamentary Secretary, gave the following figures, and said that the pattern was not even all over the country:

Welfare Food	Period		
	Jan.–June, 1954	July–Dec., 1954 (27 Weeks)	Jan.–June 1955 (26 Weeks)
National dried milk (millions of tins)	11·92	11·33	10·12
Cod-liver oil (millions of bottles)	3·30	2·79	2·64
Vitamin A and D tablets (millions of packets)	1·03	0·83	0·98
Orange juice (millions of bottles)	14·81	13·41	13·80

She was going further into the reasons for the fall in demand for National dried milk, some of which was offset by the purchase of proprietary brands.

Road Accidents and Alcohol

Mr. GEORGE THOMAS (Cardiff, West, Lab.) asked the Minister of Transport on November 2 what action he had taken to warn the public about the close relation between road accidents and the drinking of alcohol. Mr. J. BOYD-CARPENTER answered: by publishing the message inside the front cover of the Highway Code. Mr. THOMAS asked for further consideration to be given to the matter. Mr. BOYD-CARPENTER reminded him that Professor Drew, of Bristol University, and the Medical Research Council were conducting an investigation into this difficult problem. He would prefer not to say anything more about it until he had the report. Mr. SOMERVILLE HASTINGS (Barking, Lab.) said that hoardings were covered with advertisements saying how valuable alcohol was under various conditions. Could not

something be done about it? Mr. BOYD-CARPENTER pointed out that he had nothing to do with advertisements on hoardings.

Food Hygiene.—It is intended to issue the new regulations on food hygiene as soon as the consolidation Bill on food and drugs legislation becomes law—the Minister hopes, during November.

Health Service Costs.—The Minister of Health expects to receive the report of the Guillebaud Committee within the next six weeks.

Closed Beds.—At the end of 1954 there were 14,984 beds in general hospitals and 2,059 in mental hospitals that were closed because of staff shortage.

Limbless Pensioners.—The number of limbless pensioners of the 1914–18 war receiving one or more of the four main supplementary allowances—for unemployability, constant attendance, comforts, and lowered standard of occupation—is about 2,100, of whom about 700 are 65 years of age or over.

Vital Statistics

Poliomyelitis

In the week ending October 29 the total number of cases of acute poliomyelitis in England and Wales decreased by 18, the paralytic cases decreasing by 21. The figures for the week (with those for the previous week in parentheses) were: paralytic 189 (210), non-paralytic 140 (137), total 329 (347). Deaths in the great towns numbered 11. Notifications from the beginning of the year up to October 29 numbered 6,030. In 1947 and 1950, the only two years in which they have been more numerous, they amounted to 8,027 and 7,557.

The incidence of the disease increased slightly in the northern, southern, and midland regions, and in Wales. It decreased in the East and West Ridings of Yorkshire, and in the north-midland, eastern, London and south-eastern, south-western and north-western regions. The following districts have had particularly high rates to date (figures for cases notified up to October 29, with rates per 100,000 population in parentheses): Mexborough U.D. 22 (115.7), Barnsley C.B. 79 (105.5), Cheshunt U.D. 25 (98.6), Willesden M.B. 168 (94.7), Walton and Weybridge U.D. 37 (92.0), and Hoyland Nether U.D. 13 (81.9).

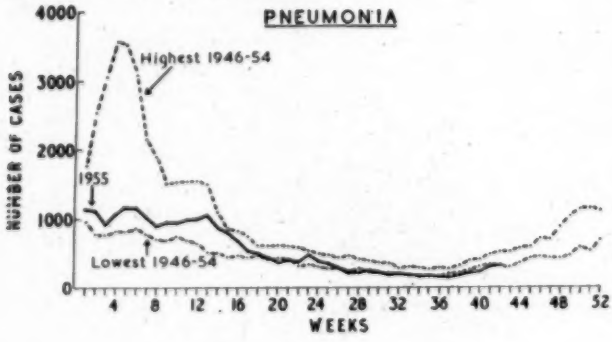
In Scotland 27 cases were notified, a decrease of 21 from the previous week's total. 14 of them were reported from Glasgow, 17 fewer than in the previous week.

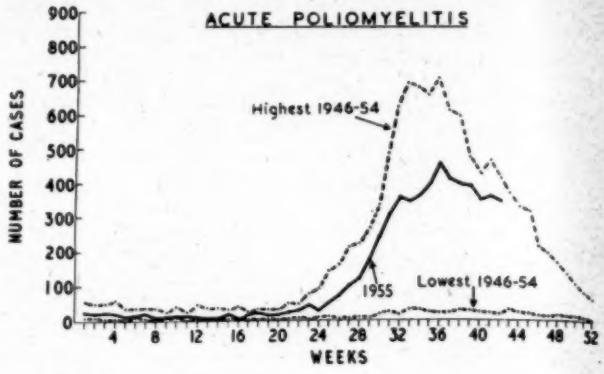
Week Ending October 29

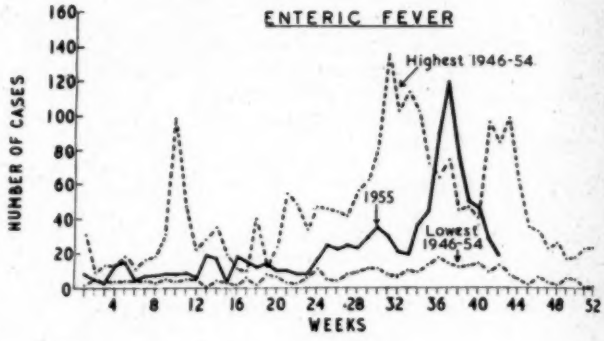
The notifications of infectious diseases in England and Wales during the week included: scarlet fever 888, whooping-cough 833, diphtheria 11, measles 2,301, acute pneumonia 329, acute poliomyelitis 329, dysentery 474, and paratyphoid fever 12.

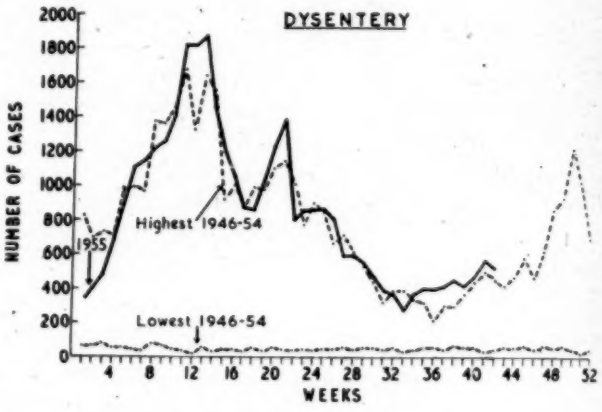
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figure. reported in each week during the nine years 1946–54 are shown thus ------, the figures for 1955 thus ———. Except for the curves showing notifications in 1955, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

The only large variations in the trends of the notifications of infectious diseases in England and Wales during the week ending October 22 were increases of 366 for measles, from 1,750 to 2,116, and 38 for scarlet fever, from 729 to 767, and a decrease of 54 for dysentery, from 577 to 523.

The largest increase in the incidence of measles was 68 in Devonshire, from 107 to 175; this rise was mainly contributed by Exeter C.B., where the notifications rose from 26 to 77. The largest rise in the number of notifications of scarlet fever was 37 in Yorkshire West Riding, from 84 to 121. 817 cases of whooping-cough were notified, being the same number as in the preceding week; only small fluctuations were recorded in the local trends. 13 cases of diphtheria were notified, being 5 more than in the preceding week. 5 cases were notified in Lancashire (Liverpool C.B. 3) and in London (Shoreditch 5).

The largest returns of dysentery were Lancashire 134 (Liverpool C.B. 48, Haslingden M.B. 18, Manchester C.B. 9, Preston C.B. 9), Yorkshire West Riding 72 (Leeds C.B. 22, Huddersfield C.B. 19), London 50 (Stepney 16), Sussex 45 (Shoreham-by-Sea U.D. 21, Brighton C.B. 20), Warwickshire 37 (Birmingham C.B. 27), Surrey 18 (Godstone R.D. 10), and Middlesex 18.

In Scotland the notifications of dysentery rose from 218 to 252. The largest returns were Glasgow 156, Dundee 16, Lanark county 16, Aberdeen county 13, and Edinburgh 12.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **October 22** (No. 42) and corresponding week 1954.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1955					1954				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	13	5	4	1		23	3	2	0	
Dysentery	523	50	252	14	5	454	43	183	9	
Encephalitis, acute	6	1		0		4	1		0	
Enteric fever:										
Typhoid	2	0	0	1		7	0	0	1	
Paratyphoid	17	1	1	3	2(B)	6	0	1(B)	0	
Food-poisoning	302	26		0		181	56		2	
Infective enteritis or diarrhoea under 2 years				16	45				21	14
Measles*	2,116	33	30	11	20	3,454	204	447	79	143
Meningococcal infection	20	1	7	0		38	4	7	0	
Ophthalmia neonatorum	44	3	9	0		36	2	7	0	
Pneumonia†	304	29	139	3		400	24	117	2	2
Poliomyelitis, acute:										
Paralytic	210	27	48	2	8	39	4	26	1	1
Non-paralytic	137	22				23	0			
Puerperal fever§	252	28	9	1		265	44	12	1	1
Scarlet fever	767	55	120	24	33	749	48	161	23	33
Tuberculosis:										
Respiratory	622	59	120	22		794	63	135	43	
Non-respiratory	85	6	23	5		122	8	15	10	
Whooping-cough	817	38	57	82	83	1.544	86	213	12	36

DEATHS in Great Towns	1955					1954				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	1	0	1	0	0	0	0
Dysentery	0	0	1	1		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	9	0	1	1	1	8	0	2	0	0
Influenza	5	0	0	0	1	6	0	0	0	0
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	1				0	0		
Pneumonia	169	27	13	13	7	156	27	24	13	7
Poliomyelitis, acute	10	1			0	2	0			0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	60	6	6	0	5	68	6	10	0	7
Non-respiratory		0	0	1	1		2	10	2	0
Whooping-cough	0	0	0	0	1	1	0	0	0	0
Deaths 0–1 year	176	24	24	9	17	186	28	29	7	15
Deaths (excluding stillbirths)	4,798	743	500	90	153	4,665	691	567	87	167
LIVE BIRTHS	7,020	1016	935	202	318	7,155	1151	832	225	490
STILLBIRTHS	173	18	13			173	18	20		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Cortisone and Hydrocortisone.—Arrangements made by the Ministry of Health and the Department of Health for Scotland with manufacturers of cortisone and hydrocortisone will enable preparations of these drugs (for oral, parenteral, and topical use) to be freely prescribable by the medical profession in the United Kingdom from December 5. These arrangements do not apply to corticotrophin (A.C.T.H.) and certain steroid substances such as prednisone and prednisolone, which, for the time being, will continue to be supplied only through hospitals. A leading article on the subject of cortisone is published in this issue at p. 1194.

College of Physicians and Surgeons of South Africa.—The final stages in the launching of the College of Physicians and Surgeons of South Africa have now been reached. Last July the College was incorporated. Until January 17 it will remain possible for doctors on the South African *Register* to join as associate founders by payment of a fee, but after that date all admissions will be by examination. The electorate of founders and associate founders will then proceed to elect the first College council. The College is established to promote the study and practice of medicine and the allied arts and sciences, and to maintain the highest standards of professional conduct. The College will examine, and research and postgraduate teaching are envisaged in the future. The Medical Association of South Africa has played a notable and generous part in the College's foundation. Five years ago the federal council of the Medical Association of South Africa, then considering ways of improving postgraduate education, voted to establish a college. The association backed the project with the resources of its own organization and experience, a working subcommittee, offices, and money. By May, 1954, matters had progressed sufficiently for an inaugural meeting of founder members of the College to be held. A steering committee was elected, and the association relinquished the management of the College's affairs in its favour.

Nobel Prize for Chemistry.—The Swedish Academy of Science announced last week that this year's Nobel Prize for Chemistry would be awarded to Professor VINCENT DU VIGNEAUD, of Cornell University Medical College, for his work on the synthesis of hormones secreted by the posterior pituitary gland. Professor du Vigneaud and his co-workers described the synthesis of oxytocin in 1953—the first synthesis of a polypeptide hormone. Oxytocin, which is the principal uterine-contracting and milk-ejecting hormone, can be thought of as a cyclic polypeptide and side-chain, with a cystine residue as its key component. Professor du Vigneaud first deduced its structure by chemical reasoning, and then went on to synthesize it. Biological tests showed that the activity of the synthetic preparation was comparable with that of the natural hormone. Professor du Vigneaud has also synthesized vasopressin, which raises the blood pressure and possesses antidiuretic activity. Vasopressin is closely related to oxytocin, but there are species differences in composition, and it was lysine vasopressin which was first synthesized. Professor du Vigneaud, who was born in Chicago in 1901, has been head of the department of biochemistry at Cornell University Medical College since 1938. At one time he worked on the chemistry of penicillin, and in 1948 he was honoured by the Award of Merit for war research.

Iveagh Chair of Chemical Microbiology, Oxford.—A new Chair of Chemical Microbiology has been established at Oxford, thanks to a generous offer of £668 a year for 21 years by Arthur Guinness, Son & Co., Ltd., the brewers, towards the cost of it. Dr. D. D. WOODS, F.R.S., Guinness research fellow and reader in microbiology at Oxford, has been appointed the first holder of the Iveagh Chair of Chemical Microbiology. Dr. Woods, who is 43, is best

known for his work with Sir Paul Fildes, when a member of the Medical Research Council's bacterial chemistry research unit, on the mode of action of sulphanilamide. Their work on competitive enzyme blockers first gave a rational basis to the search for new chemotherapeutic agents.

Mental Health Exhibition.—The Ministers of Labour and National Service and of Health joined on November 7 in opening a mental health exhibition at Central Hall, Westminster, with the twin objects of dispelling public misconceptions on mental illness and mental deficiency and of stimulating recruitment to mental nursing. The exhibition, which remains in London until November 12 and then goes on tour, includes a photographic display to illustrate something of the nature of mental illness, its treatment, and nursing; demonstrations of nursing techniques and equipment; apparatus such as the electroencephalograph; models of new mental hospitals; and a number of "free expression" drawings by patients. Sir WALTER MONCKTON (Minister of Labour and National Service) said that, while in recent years there had been a striking increase in the number of trained nurses, the picture in the mental field was by no means so rosy. The fact that nearly half the hospital beds in Britain were in mental or mental deficiency hospitals underlined the importance of the problem. The Minister of Health, Mr. IAIN MACLEOD, said that, even more than new buildings or new staff, a new attitude to mental health was needed: "Mental illness is something neither to be feared nor to be shunned, but to be understood." Since the start of the Health Service, he continued, partly by reallocation of beds and partly through the provision of new ones, something like 9,000 extra beds had been made available for mental cases; there were also short- and long-term plans for a further 11,500 beds, making some 20,000 in all.

Award for Gallantry.—On June 16, 1955, Surgeon Lieutenant CHARLES ERIC RHODES lost his life while trying to save men trapped in H.M. Submarine *Sidon*, which sank in Portland Harbour after an explosion. The QUEEN has now approved the posthumous award of the Albert Medal to Surgeon Lieutenant Rhodes for gallantry in saving life at sea. The citation in the *London Gazette* (November 1) states that he "was among the first to enter the *Sidon* after the explosion and, in spite of the total darkness and dense smoke, he brought out an injured man to safety. He then put on a Davis submarine escape apparatus and re-entered the submarine with morphia to give further help to the injured. In doing so he greatly prejudiced his chance of escape. He was not a submarine officer and was not familiar with the use of the breathing apparatus or the lay-out inside a submarine. In spite of these handicaps and the pitch darkness his only thoughts were for those within the submarine; he had no hesitation in re-entering the *Sidon*, and he succeeded in helping two more men to escape before the submarine sank. Surgeon Lieutenant Rhodes's gallant and selfless act in helping to save the lives of others cost him his own life."

Royal College of Physicians of Edinburgh.—Dr. WILLIAM NORMAN PICKLES, of Aysgarth, Yorkshire, was admitted to the Honorary Fellowship of the Royal College of Physicians of Edinburgh on November 1. The vice-president of the College, Dr. RAE GILCHRIST, introducing Dr. Pickles to the Fellows, spoke of the great contributions which he had made to general practice. At the same meeting of the College Dr. Pickles was awarded the James Mackenzie Medal, which is given at the discretion of the Council of the College to the physician engaged in family practice who has made the greatest contribution to medical science. This is the first time this medal has been awarded.

Wiltshire Memorial Research Scholarship.—Registered medical practitioners are invited to apply to the Dean of King's College Hospital Medical School, London, S.E.5, for details of this scholarship. It is for research in cardiology in its broadest sense, and carries an honorarium of at least £400 a year; it may be held part-time and applied to study abroad.

Copley Medal.—The Royal Society's Copley Medal has been awarded to Sir RONALD FISHER, F.R.S., professor of genetics at Cambridge, for "his distinguished contributions to developing the theory and application of statistics for making quantitative a vast field of biology."

Grenfell Association's Christmas Cards.—This year the Grenfell Association is selling Christmas cards to raise funds for an ambulance for the association's medical work in Labrador and Northern Newfoundland. Now that roads are being developed to link the association's headquarters at St. Anthony with the northern outposts, the need for an ambulance is urgent. An illustrated leaflet of the Grenfell cards will be sent on receipt of 1½d. to the Grenfell Association, 66, Victoria Street, London, S.W.1.

Sir Henry Cohen, professor of medicine at Liverpool since 1934, has been invited by the Birkenhead Town Council to accept the Freedom of the borough. Sir Henry was born in Birkenhead in 1900 and received his early education there.

Dr. E. A. Carmichael, physician at the National Hospital for Nervous Diseases, Queen Square, and director of the M.R.C. Neurological Research Unit, has been appointed chairman of the British Council's medical panel in succession to the late Sir Edward Mellanby.

COMING EVENTS

Induced Hypotension in Anaesthesia.—A fortnight's course on "Induced Hypotension in Anaesthesia" is being held at the department of anaesthesia, Royal Infirmary, Edinburgh, from January 9 to 20. For further details, see our advertisement columns at p. 58.

Fourth International Congress on Diseases of the Chest.—This congress, which is sponsored by the American College of Chest Physicians, will be held in Cologne, Germany, August 19–23, 1956. Those wishing to present papers should inform Professor A. L. BANYAI, American College of Chest Physicians, 112, East Chestnut Street, Chicago, 11, without delay.

NEW ISSUES

Annals of the Rheumatic Diseases.—The next issue (Vol 14, No. 3) is now available. The contents include:

LORD HORDER.
DIPHENYLAMINE REACTION IN RHEUMATOID ARTHRITIS. G. R. Fearnley, Jeanette Pirkis, Nanette de Coek, Rita Lackner, and R. I. Meanock.
ORAL HYDROCORTISONE THERAPY IN RHEUMATOID ARTHRITIS. Edward W. Boland.
SHORT REVIEW OF CONNECTIVE TISSUE METABOLISM. H. G. B. Slack.
AGGGLUTININS AND INCOMPLETE ANTIBODIES AFTER A SINGLE ANTIGENIC INOCULATION IN NORMAL AND RHEUMATIC INDIVIDUALS. Vladimír Wagner and Václav Rejholec.
METACORTANDRACIN AND 9-ALPHA-FLUORO HYDROCORTISONE ACETATE IN RHEUMATIC DISEASES. L. Villa, C. B. Ballabio, and G. Sala.
CHRONIC ARTHRITIS AFTER RECURRENT RHEUMATIC FEVER. A. E. Thomas.
SERUM DIPHENYLAMINE REACTION IN RHEUMATOID ARTHRITIS. Elvio Cecchi and Fabrizio Ferraris.
RHEUMATOID ARTHRITIS AND PLASMACYTOMATOSIS. Tomaso Galli and Enrico Chiti.
PARAFFIN-WAX BATHS IN THE TREATMENT OF RHEUMATOID ARTHRITIS. R. Harris and J. B. Millard.
SERIAL STUDIES OF SYNOVIAL FLUID IN EVALUATING INTRA-ARTICULAR AGENTS. Frank K. Austen and Evan Calkins.
STUDIES OF THE ACID POLYSACCHARIDE OF THE WHITE CELLS IN RHEUMATIC AND OTHER DISEASES SHOWING ITS SIMILARITY TO THE ACID POLYSACCHARIDE OF AMYLOID. M. Bassiouni.
EFFECT OF CORTISONE AND CERTAIN OTHER STEROIDS ON THE PERIPHERAL VASCULATURE IN ARTHRITIS. A. Woodmansey and J. W. Beattie.

Issued quarterly; annual subscription £2 2s.; single copy 12s. 6d.; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

Abstracts of World Medicine.—The November issue (Vol. 18, No. 5), which is now available, contains abstracts of important papers drawn from medical and other scientific journals published in some 20 different countries and in all five continents. The subjects covered range over the whole field of clinical medicine and include pathology, microbiology and parasitology, pharmacology, and chemotherapy: there are also sections dealing with industrial medicine, forensic medicine and toxicology, anaesthetics, radiology, and the history of medicine.

Issued monthly; annual subscription £4 4s.; single copy 8s. 6d.; a specimen will be sent free on request to the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, November 14

INSTITUTE OF PSYCHIATRY.—5.30 p.m., Dr. E. Stengel: postgraduate lecture-demonstration.

SOCIETY OF APOTHECARIES OF LONDON.—4.30 p.m., Mr. S. Oram: Valvular Disease of the Heart, with special reference to Cases for Operation; 5.45 p.m., Sir Russell Brock: Surgery of Valvular Disease of the Heart.

SOUTH-WEST LONDON MEDICAL SOCIETY.—At Rembrandt Hotel, 8 for 8.30 p.m., annual dinner.

UNIVERSITY COLLEGE LONDON: DEPARTMENT OF PHARMACOLOGY.—At Physiology Theatre, 5.30 p.m., Dr. W. S. Feldberg, F.R.S.: Recent Experiments on the Pharmacology of the Periventricular Grey Matter of the Brain.

Tuesday, November 15

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor R. E. Tunbridge: Observations on the Structure of Connective Tissue Fibres.

ILFORD MEDICAL SOCIETY.—At King George Hospital, 9 p.m., Dr. L. Crome: A British Doctor Visits Russia (with slides). Members of the Stratford Division, B.M.A., are invited.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. J. A. Dudgeon: Viral Diseases of the Skin.

●INSTITUTE OF NEUROLOGY.—5.30 p.m., Dr. P. H. Sandifer: Pain in the Neck and Upper Limbs.

●OXFORD UNIVERSITY MEDICAL SOCIETY.—At Radcliffe Infirmary, 8.15 p.m., Professor B. Katz, F.R.S.: The Least Quantum of Neuromuscular Transmission.

ROYAL ARMY MEDICAL COLLEGE.—5 p.m., Sir Owen Wansbrough-Jones: The Medical Services and New Weapons.

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Charles West Lecture by Dr. W. P. H. Sheldon: Coeliac Disease.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—3.45 p.m., Arnott Demonstration by Dr. F. Stansfield: Anatomy of the Visual Pathway.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Theatre, 5 p.m., Mr. J. H. Peel: Diabetes and Pregnancy.

SOCIETY FOR THE STUDY OF ADDICTION.—At Medical Society of London, 8 p.m., symposium: Smoking and Cancer. Speakers, Dr. Horace Joules, Sir Adolphe Abrahams, Mr. K. S. Mullard, and Professor Sidney Russ.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. N. G. Hulbert: neurological demonstration.

Wednesday, November 16

BRITISH DENTAL ASSOCIATION: MIDDLESEX AND HERTFORDSHIRE BRANCH: ACTON, EALING, AND CHISWICK SECTION.—At Paul's Restaurant, New Broadway, Ealing, W., 8 p.m., ordinary meeting, in conjunction with West Middlesex Division, B.M.A. Dr. J. C. Houston: Problem of Bleeding.

COLLEGE OF GENERAL PRACTITIONERS.—At Worcester Royal Infirmary, 3.30 p.m., Dr. E. N. Moyes: Early Diagnosis of Tuberculosis.

EUGENICS SOCIETY.—At Royal Society, Burlington House, W., 5.30 p.m., Dr. H. C. Maurice Williams: Problem Families in Southampton.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. J. A. Dudgeon: Viral Diseases of the Skin.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. C. Hoyle: Sarcoidosis.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Professor F. C. Ormerod: Plastic Surgery of the Middle Ear.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. F. R. Kilpatrick: Tuberculosis of the Renal Tract.

LIVERPOOL UNIVERSITY.—At Surgery Theatre, Medical School, 5.15 p.m., Lady Jones Lecture in Orthopaedic Surgery by Professor R. I. Harris: Hypermobile and Rigid Flat Feet.

LONDON COUNTY MEDICAL SOCIETY.—At Belmont Hospital, Brighton Road, Sutton, Surrey, 2.30 p.m., meeting.

MIDDLESEX COUNTY MEDICAL SOCIETY.—At West Middlesex Hospital, Isleworth, 3 p.m., meeting.

MIDLAND MEDICAL SOCIETY.—At General Hospital, Birmingham, 8.15 p.m., clinical meeting.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. G. J. Popjak: Fat Metabolism.

RESEARCH DEFENCE SOCIETY.—At Physiology Lecture Theatre, University College, W.C., 5.30 p.m., 24th Stephen Paget Memorial Lecture by Sir Henry Dale, O.M., F.R.S.: Humanity's Rising Debt to Medical Research.

ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW.—5 p.m., Professor J. N. Davidson: Biochemical Approach to Cell Structure in Health and Disease.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Dr. P. A. Tyser: Public Awareness of Public Health.

ST. MARYLEBONE HOSPITAL FOR PSYCHIATRY AND CHILD GUIDANCE.—5.30 p.m., Dr. Colman Kenton: Techniques of Contemporary Physical Treatments.

SOCIETY OF APOTHECARIES OF LONDON.—5.30 p.m., First Gideon De Laune Lecture in Commemoration of the Founder of the Society by Sir Zachary Cope: The Society of Apothecaries and Medical Education—A Historical Survey.

Thursday, November 17

BRITISH INSTITUTE OF RADIOLOGY.—8 p.m., Mr. W. G. Clarke: Significance of Film and Screen Speed Variation.

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor N. H. Martin: Some Aspects of Protein Diseases.

EDINBURGH CLINICAL CLUB.—At Royal College of Physicians of Edinburgh, 8 p.m., Professor John Crofton: Present Trends in Pulmonary Tuberculosis.

HONYMAN GILLESPIE LECTURES.—At University New Buildings, Teviot Place, Edinburgh, 5 p.m., Professor G. MacG. Bull: Diagnosis and Treatment of Disturbances of Water and Electrolytes.

INSTITUTE OF NEUROLOGY.—5 p.m., Dr. Margaret Kennard (Canada): Study of Electroencephalographic Frequency Patterns as Related to Behaviour.

LIVERPOOL MEDICAL INSTITUTION.—8 p.m., Mr. H. J. B. Atkins: Modern Views on Treatment of Carcinoma of the Breast.

LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At 11, Chandos Street, W., 8.30 p.m., Dr. A. E. Clark-Kennedy: Interpretation of Symptoms.

●LONDON MARRIAGE GUIDANCE COUNCIL.—At National Association for Mental Health, 7 p.m., Dr. J. F. L. Barnes: Paranoia and Paranoid States in Marriage.

MANCHESTER MEDICAL SOCIETY.—At Manchester University, 8 p.m., Section of Anaesthetics. Dr. F. W. Oliver: Carbon Dioxide Concentrations in Anaesthetic Apparatus; Dr. E. G. Rees Jones: The Anaesthetist in Obstetrics.

NORTH-WESTERN TUBERCULOSIS SOCIETY.—At Manchester Royal Infirmary, 5 p.m., Dr. R. W. Riddell: Significance of Bacterial Resistance in the Treatment of Tuberculosis.

ROYAL EYE HOSPITAL.—5.15 p.m., Dr. T. H. Whittington: Aspects of Refraction.—6. Lenses and Their Effects; Prescription and Fitting of Spectacles.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—5.30 p.m., Blackham Lecture by Mr. H. C. Edwards: Contribution of War to the Advancement of Surgery (illustrated).

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.—At London School of Hygiene and Tropical Medicine, 7.30 p.m., laboratory meeting.

ST. ANDREWS UNIVERSITY.—At Physiology Department, Queen's College, Dundee, 5 p.m., Professor W. M. Millar: Differential Diagnosis of Organic and Functional Disorders.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. D. J. Williams: postgraduate demonstration in neurology.

Friday, November 18

BRITISH INSTITUTE OF RADIOLOGY.—6.30 p.m., Dr. E. E. Pochin and Dr. H. Miller: Discussion of Radioactive Measurements in Clinical Practice.

BRITISH TUBERCULOSIS ASSOCIATION.—At 26, Portland Place, W., 5 p.m., Dr. J. D. Dow: The Allergic Lung; Dr. E. T. W. Starkie: Calculation of Radiation Dosage During Chest Examinations; Dr. A. J. Eley: Mistaken Diagnoses.

FACULTY OF RADIOLOGISTS.—At Royal College of Surgeons of England, 5 p.m., First Crookshank Lecture by Sir Russell Brain: Some Aspects of Neurology of the Cervical Spine.

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. M. S. Thomson: Lichen Planus.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., clinical demonstration by Dr. J. L. Livingstone.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., Mr. J. C. Hogg: Epistaxis.

MANCHESTER ROYAL INFIRMARY.—At Chemistry Theatre, Manchester University, 5.15 p.m., Lloyd Roberts Lecture by Lady Violet Bonham Carter: Of Human Greatness.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 2 p.m., Mr. F. W. Holdsworth: Traumatic Paraplegia. (2) 4 p.m., Dr. D. M. T. Gairdner: Anaphylactoid Purpura—(Schoenlein-Henoch Syndrome).

ROYAL MEDICAL SOCIETY, EDINBURGH.—8 p.m., Dissertation by Mr. I. C. Crawford: Recent Advances in Anaesthetics.

Saturday, November 19

BIOCHEMICAL SOCIETY.—At Middlesex Hospital Medical School, 11 a.m., scientific papers.

APPOINTMENTS

MACFARLANE, DAVID A., M.B., B.Ch., F.R.C.S., Surgical Tutor, St. Bartholomew's Hospital, London.

NORTH-WEST METROPOLITAN REGIONAL HOSPITAL BOARD.—R. G. Miller, M.B., B.Chir., M.R.C.P., Consultant Physician, Bedford General, Clapham, Biggleswade and Steppingly Hospitals; Edith M. Taylor, M.B., B.S., F.F.A., Consultant Anaesthetist, Marie Curie Hospital; G. W. Garland, M.D., M.R.C.O.G., Consultant Gynaecologist, Bushey Hospital; A. R. Ryan, M.D., F.F.A., Consultant Anaesthetist, Hitchin hospitals; R. Paul, M.B., Ch.B., D.M.R.D., Consultant Radiologist, Royal London Homoeopathic Hospital; P. D. W. Shepherd, M.B., B.S., D.P.M., Assistant Psychiatrist (S.H.M.O.), Shenley Hospital; T. M. J. Haran, M.B., B.Ch., D.P.M., Assistant Psychiatrist (S.H.M.O.), Napsbury Hospital; B. Golberg, M.B., B.Ch., M.R.C.P., Assistant Chest Physician (S.H.M.O.), Ashford Chest Clinic; S. Felsenburg, M.D., D.P.M., Assistant Psychiatrist (S.H.M.O.), Friern Hospital; J. Merry, M.D., D.P.M., Assistant Psychiatrist (S.H.M.O.), St. Bernard's Hospital; D. Preiskel, M.D., M.R.C.P., Physician in Physical Medicine (S.H.M.O.), Hornsey Central Hospital; R. S. E. Brewerton, M.R.C.S., L.R.C.P., D.O.M.S., Ophthalmologist (S.H.M.O.), Watford School Ophthalmic Clinic; G. F. Ensor, M.R.C.S., L.R.C.P., D.O.M.S., Ophthalmologist (S.H.M.O.), Hatfield School Ophthalmic Clinic; Ann Garratt, M.B., B.S., D.O., Ophthalmologist (S.H.M.O.), Middlesex County Council School Clinic, Wealdstone; H. Caplan, M.B., B.S., Assistant Pathologist (S.H.M.O.), Northern Group of Hospitals.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Jarvis.—On October 31, 1955, at Southmead Hospital, Bristol, to Valerie, wife of Dr. D. J. A. Jarvis, a son.

Mitchelmore.—On October 31, 1955, at St. George's Hospital, Wallingford, Berks, to Una (formerly Jones), M.B., Ch.B., wife of Gordon E. Mitchelmore, M.B., Ch.B., a sister for Andrew—Helen Joanna.

DEATHS

Anderson.—On October 14, 1955, in a road accident, Catherine Grace Anderson, M.B., Ch.B., of Benvarran, Kilbarchan, Renfrewshire.

Baillie.—On October 3, 1955, at St. Mary's Hospital, London, W., William Herbert Baillie, M.R.C.S., L.R.C.P., of Shangrila, Sungkai, Perak, Malaya, aged 65.

Beaumont.—On October 10, 1955, at Sutton Coldfield Nursing Home, Owen Albert Beaumont, M.R.C.S., L.R.C.P., formerly of East Ham, London, E., aged 63

Collinson.—On October 9, 1955, in a nursing home, Walter Julius Collinson, M.B., Ch.B., D.T.M.&H., Lieutenant-Colonel, I.M.S., retired.

Hayne.—On October 12, 1955, Percy Alfred Hayne, M.R.C.S., L.R.C.P., D.P.H., of North Lea, Stone Cross, Westham, Sussex, formerly of Mandalay, Burma, aged 79.

Shenton.—On October 12, 1955, in London, Edward Warren Hine Shenton, M.R.C.S., L.R.C.P., late of Harley Street, London, W., aged 83.

Thomson.—On October 7, 1955, at Edinburgh, May Thomson, L.R.C.P.&S.Ed., L.R.F.P.S., D.P.H., formerly of 14, Harrington Gardens, London, S.W.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Should Cases of Polio Always go to Hospital ?

Q.—*Assuming good home conditions, should young children with mild attacks of acute poliomyelitis always be admitted to hospital ? Sometimes such a course would lead to psychological difficulties, and I should like to know whether there are overriding clinical or public health reasons for so doing.*

A.—There is some difference of opinion about this matter. First, from the public health point of view, there are those who maintain that all suspected cases of poliomyelitis, like cases of smallpox, should be removed to an isolation hospital in order to prevent spread of the disease ; while others maintain that these isolation endeavours have never been shown to prevent cases from occurring and that attempts to prevent spread by hospital isolation are futile.

With regard to clinical reasons, there is again some difference of opinion. On the one hand, there are those who maintain that the child might be developing tuberculous meningitis, and must therefore come in for diagnosis. On the other hand, others maintain that most cases of pre-paralytic poliomyelitis are easily distinguished from tuberculous meningitis ; and that, as there is no specific treatment for the disease, the journey to hospital only does harm. The advocates of this view maintain that the child can often be safely kept at home during the acute phase, provided always that, if he develops bulbar or respiratory weakness, he can be promptly transferred to a special respiratory centre, preferably by a mobile unit.

In the absence of decisive evidence showing which is right, the questioner must be left to make his own choice between these widely divergent views.

Physiotherapy after a Stroke

Q.—*Please give details of what physiotherapy and re-education should be given to a patient with hemiplegia following a recent stroke.*

A.—It is only in recent years that the value of early purposeful physiotherapy in the treatment of hemiplegia has been recognized. Rusk[1] states that with an intensive programme of rehabilitation 90% of hemiplegic patients can be taught to walk and to look after themselves, and 30% can undertake "gainful work."

The purposes of treatment are (1) to prevent deformities such as a frozen shoulder or a contracture of the Achilles tendon ; (2) to correct such deformities if they occur ; (3) to teach the patient to walk ; (4) to teach the patient to use the unaffected upper limb to carry out daily activities ; (5) to retrain the affected upper limb ; (6) to correct disturbances of speech.

Treatment in Bed

Attention must be paid to the general posture of the patient in bed. The back should be supported by pillows ; a pillow in the axilla on the affected side will prevent internal rotation and adduction of the arm. Pillows should not be placed under the knees if the patient has to remain in bed more than a few days, as fixed flexion deformity of hip or knee may develop. A board across the foot of the bed will help to keep the foot dorsiflexed and prevent the patient from slipping down the bed ; a bed cradle should be used to prevent clawing of the toes.

Passive movements of all joints should be performed at least twice daily, special attention being paid to movements of the ankle to prevent shortening of the tendo Achillis, and to movements of the arm to prevent a frozen shoulder. Both of these deformities may develop rapidly. A pulley may be fixed over the head of the bed with one end of a long cord tied to the affected wrist ; the cord is then passed through the pulley and a loop is made at the other end so that the patient can passively elevate the paralysed arm with his unaffected hand ; this can be repeated at frequent intervals.

Once a frozen shoulder has developed, return of movement is likely to be a matter of months and will probably not be complete. If the shoulder is not painful, exercises preceded by heat in some form may help to increase the range of movement. Local pain may be relieved by heat, counter-irritants, and analgesics. A tight Achilles tendon should be stretched passively, and operation is seldom required at this stage.

General Management

Except in severe cases it is probably safe to get the patient up soon after he has recovered consciousness, certainly within 24 hours. The patient sits on a stool at the end of the bed, the paralysed hand being placed on the bed rail with the good hand ; the patient then stands up and sits down 5 to 10 times, repeating the exercise after a rest period.

The patient should start to walk as early as possible—after the first day or two—in a mild case of hemiplegia following cerebral thrombosis. The normal person when he walks moves the right arm and left leg forward and then the left arm and right leg. The hemiplegic, on the other hand, walks with the affected arm motionless at the side with forearm flexed ; he keeps the knee fixed and circumducts the leg, making walking difficult and painful. A calliper with short bilateral steels, 90° ankle-stop, and supinator T-strap will prevent the foot turning over and is a great help in walking. Retraining in walking is best carried out between parallel bars, fitted with a sliding part over the bars to prevent excoriation of the hands. Later the patient can be put into the walking-chair, or walk with the aid of elbow crutches or sticks. Mild hemiplegics can often walk without any aids.

A right-handed person is seriously handicapped by a right hemiplegia, and training in use of the left hand for the simple activities of daily life such as washing and dressing should be started as soon as possible. Left-hand writing must be practised, especially if aphasia is present.

Training of the affected arm should start at the same time. Difficult movements are external rotation at the shoulder and flexion-extension at the elbow. Active pronation and supination of the forearm and extension of the fingers are usually impossible. The severity of the stroke, age, and mentality of the patient will largely determine the result. Simple exercises carried out 5 to 10 times hourly include : (1) Flexion of the arm at the shoulder : the patient grasps the wrist of the affected arm with the other hand and raises it as far forwards and upwards as possible. (2) Flexion and extension at the elbow : if a hemiplegic patient is asked to flex the elbow he will usually abduct the arm at the shoulder and rotate it internally. If the patient sits in a chair, however, with elbows close to the side, palms pressed close together, and rests the ulnar border of the forearms on the affected knee, he can flex the elbows and touch his chin without abducting the arm. (3) Flexion of the forearm and arm of the affected side : the patient sits on a chair in front of a table. Without elevating or abducting the shoulder the patient flexes the forearm to table level and then flexes the arm, placing his elbow on the table. If the wrist is held in a flexed position a small plaster cock-up splint should be used to keep the hand dorsiflexed to 20°. The fingers of a spastic hemiplegic patient cannot be re-educated to any useful purpose, but the fingers should be passively extended with the other hand or by pressing the affected hand flat on a table several times a day if flexion contractures of the fingers are to be avoided.

The most difficult problem perhaps in the management of the hemiplegic is aphasia, especially in the aged and, rather

surprisingly, in patients of education and intelligence. An experienced speech therapist may be able to help.

It is important to realize that some hemiplegics will have little residual disability while others are aphasic and paralysed. In a few patients recovery is slow in the first few weeks, but progress is more rapid later and some recovery of function may take place any time during the first six months.

REFERENCE

1 Rusk, H. A., *Hemiplegia and Rehabilitation*, 1953, Institute of Physical Medicine and Rehabilitation, New York University, Bellevue Medical Centre.

Injections and Poliomyelitis

Q.—*It appears to be the generally accepted practice nowadays that immunization of infants should cease during outbreaks of poliomyelitis. This, I presume, is because of the risk of a paralysis selecting the traumatized muscles. (1) Would it then be a safe practice to continue immunization provided the newer suspended prophylactics are used, since these can be given subcutaneously? (2) If muscle trauma is such an important factor at these times, should other intramuscular injections also cease where possible: in particular, should penicillin injections give way to oral therapy with one or other of the antibiotics in cases where these would be equally effective?*

A.—The occasional paralysis after inoculation seems to depend on a reflex effect on the circulation of the spinal cord, and the less irritating the injection the better. The subcutaneous route unfortunately does not provide complete safety against paralysis.

There have been many cases of poliomyelitis with localized paralysis following even penicillin injections; so much so that oral therapy should certainly be used wherever possible during outbreaks of poliomyelitis.

Undescended Testicles

Q.—*There is a certain amount of confusion in the minds of most doctors about what to do when they come upon a case of undescended testicles in a boy under the age of 12 years. I should be obliged if you would let me have some advice on this point, particularly with regard to schoolchildren.*

A.—There is a most unfortunate difference of opinion between surgeons and endocrinologists as to the correct treatment of undescended testicles, which makes it very difficult to give a clear line of treatment. The confusion is chiefly due to the difficulty of knowing whether a testicle would have descended spontaneously or not, and partly to the difficulty in assessing the functional result. Acceptable data on which to decide when and how treatment should be carried out are really very scanty, although in time to come the results of testicular biopsy at the time of operation may give some valuable information.

A few general statements are worth repeating, even if they seem obvious. A testicle which is not in the scrotum may be retractile and capable of entering the scrotum at times, and will eventually come down normally. It should be possible to exclude this condition by careful and, if necessary, repeated examination. A testicle may be ectopic and have passed into the perineum or up alongside the inguinal canal, and will then not come down without treatment. Finally, a testicle may lie within the inguinal canal or the abdomen, and in either situation be impalpable, but be capable of descent at any time until the age of puberty. Undescended testicles are fairly common in boys up to the age of 3 or 4, and thereafter become progressively less common.

The expectation of spontaneous descent becomes progressively less likely with each year of life, and at the same time the possibility of testicular atrophy and impairment of spermatogenesis increases. Treatment should therefore be instituted as soon as the likelihood of spontaneous descent becomes remote and before any degree of testicular damage has occurred. It seems fairly generally accepted that spermatogenesis is likely to be affected if the testis is not within the scrotum by the age of 10, while a little evidence so far provided by testicular biopsy suggests that there may be some atrophy by the age of 4. Operative measures are, however, easier in the older child, and the general but not universal preference at the present day seems to be to leave treatment until the child is about 9.

Surgical treatment will almost certainly be needed for the ectopic testis, but, despite the misgivings of many surgeons, for the undescended testis there seems to be no harm at all in giving a course of chorionic gonadotrophic hormone. Excessive dosage is harmful, but a six-weeks course of this hormone, 500 units intramuscularly twice weekly, is safe and may well be effective. Surgical treatment is indicated if this fails, although in the case of the intra-abdominal testis this may consist in its removal, as the cord is often too short to permit it to lie within the scrotum.

To sum up, there seems nothing to lose by trying the effect of hormone therapy before proceeding to surgery. Treatment should certainly take place by the age of 10, and there is some evidence that it may be wiser to institute it much earlier.

Antihistamines in Measles

Q.—*Have antihistamines any place in the palliative treatment of measles?*

A.—There is no sound theoretical basis for the palliative treatment of measles by antihistamines. The drugs have their use in allergic rhinitis and conjunctivitis, but there is no evidence that these symptoms in measles are allergic in nature. I have found no references to published work on this subject.

Status Asthmaticus

Q.—*I have recently had a fatality from status asthmaticus in general practice. (a) What is the immediate cause of death? (b) What are the indications for removal to hospital in such a case? (c) What is the best treatment?*

A.—The cause of death in asthma is asphyxia due to widespread plugging of the bronchi with a thick gelatinous secretion.

Admission to hospital would be advisable when the treatment at home fails to ease a severe and persistent attack and when such an attack constitutes a threat to life. In considering admission into hospital one must bear in mind that death from asthma is not a rarity, for it causes almost 3,000 deaths annually in England and Wales. Further, the type of asthmatic especially at risk is the chronic asthmatic, subject to recurrent status asthmaticus. Some 80 to 90% of all asthma deaths occur in those over 30 years of age, so that it is the middle-aged and elderly that are especially at risk. Clinically, assessment of the degree of severity of an asthmatic attack is notoriously difficult, but careful and frequent attention to the pulse rate is important. I would suggest that admission to hospital should be considered in any case of status asthmaticus which fails to respond to repeated injections of adrenaline. If intravenous aminophylline also fails, then there is no doubt that urgent admission is indicated.

The generally accepted treatment for status asthmaticus is adrenaline (1 in 1,000), 5 to 10 min. (0.3 to 0.6 ml.) subcutaneously, at intervals of 15 to 20 minutes for an hour or so. Exactly how much adrenaline should be given, and for how long, is a matter of opinion, but once it becomes obvious that adrenaline is ineffective a slow intravenous injection of aminophylline (0.5 g. in 20 ml.) is indicated. When severe asthma continues, a slow intravenous drip of 5% glucose-saline with 1 g. of aminophylline per litre is set up, and three litres given over 24 hours. Morphine is contra-indicated and paraldehyde is used as a hypnotic.

When these measures fail corticotrophin or cortisone should be given. For how long intravenous aminophylline should be persevered with depends on the availability of these hormones. Their strikingly beneficial effect in severe asthma is such that they may well become the standard treatment of status asthmaticus when early relief is not obtained

by adrenaline and aminophylline, subject, of course, to special assessment and proper exclusion of those cases with a history of peptic ulceration or other contraindications. Antibiotics should be given in cases of status asthmaticus whenever the infective factor is dominant, as it so often is.

Local Reaction after A.P.T.

Q.—*Two or three weeks ago I immunized a child aged 10 months against diphtheria with alum-precipitated toxoid (A.P.T.). I gave him 0.2 ml. subcutaneously for the first injection. A few days later his mother brought him to see me, when he had a local reaction—i.e., a hard lump and surrounding erythema. Do you advise giving the usual second injection of 0.5 ml.?*

A.—Alum-precipitated toxoid (A.P.T.) is a relatively insoluble prophylactic which forms a depot on injection, represented by a hard lump or nodule with a surrounding area of leucocytic infiltration. This local tissue reaction to the material may be an essential factor in the excellent immunity which is usually observed. Owing to the very slight risk of an associated paralytic poliomyelitis, many experts now advise the subcutaneous rather than the intramuscular route of injection. When A.P.T. used to be given intramuscularly, the insoluble depot was less easily palpable, and therefore less likely to be a source of anxiety to the mother, than it is to-day.

A child aged 10 months should usually receive 0.5 rather than 0.2 ml. for the first injection. In the unusual event of an untoward reaction, the second dose four weeks later could then be 0.2 ml. As the infant in question has received only 0.2 ml., he should be given either 0.5 ml. as the second dose, or possibly two further injections each of 0.2 ml. at monthly intervals. The choice of procedure might be based on the speed with which the reaction to the first dose disappears. But the doctor should bear in mind that the first injection may have worried the mother only because it was given too superficially.

The above recommendations also apply to other suspensions of this type—e.g., purified toxoid aluminium phosphate (P.T.A.P.).

Factors Influencing Differential Leucocyte Count

Q.—*What are the known factors which may alter the differential leucocyte count in the physically fit? An inverse proportion of polymorphs to lymphocytes is often seen in the same individual at different routine blood examinations. The persons examined are chemical process workers, and allowance for experimental error, exercise, and food ingested does not seem to be the full answer, as the inversion occurs with some but not with all of the group.*

A.—In assessing changes in the differential leucocyte count it must be first remembered that the margin of error when some four hundred cells are enumerated is ±5%, and of course if only one hundred cells are counted it is much more. However, when these often unconsidered errors are excluded there are still a number of so-called physiological variations in the leucocyte count in healthy persons from day to day or hour to hour. Most of these changes are believed to be due to redistribution of the cells in the vascular channels of the body. Muscular exercise, food intake, cold winds, mental exercise, emotion, exposure to ultra-violet light, all may alter the differential count, the degree depending on the combination of factors at the particular time and to some extent on susceptibility of the person himself.

There is no doubt that the neutrophil count is appreciably raised between the hours of noon and 3 p.m. It is considered best to carry out all comparative counts in chemical workers between the hours of 10.30 a.m. and 11.30 a.m., as this is both the most stable and usually a convenient time for examination.

Cervicitis and Dysmenorrhoea

Q.—*Does low-grade chronic cervicitis ever cause dysmenorrhoea?*

A.—No, unless the cervicitis is part of a generalized pelvic infection, one of the symptoms of which may be dysmenorrhoea of the congestive type.

NOTES AND COMMENTS

Headaches in Hypertension.—Dr. I. McD. G. STEWART (Blackpool) writes: In "Any Questions?" on October 15 (p. 980) a correspondent asks about "headache and hypertension." The answer states that such headache may be of three types: (1) A vague headache accompanying anxiety; (2) migraine headaches during developing hypertension; (3) headache that may presage encephalopathic seizure. It seems to me that this categorization requires a further word about relative incidence. The term "hypertension," too, needs definition. Let it be assumed that it implies severe disease. The findings of an investigation into the subject of headache and hypertension were published in 1953.[1] A study was made of 200 consecutive patients whose diastolic pressures never, on any of several occasions under standard conditions of rest, fell below 120 mm. Hg, the average value being 136 mm. Hg. Patients aware of and unaware of headache were compared. The severity of the disease proved to be roughly the same in the two groups. Of the 104 patients who were unaware of their hypertension only three volunteered headache. Of the remaining 96 patients, all being aware of their hypertension, 71 complained of headache, mostly in terms characteristic of anxiety; nearly all the remainder had overwhelming cause, such as crippling angina or cancer, for complaining of something else. It seemed that hypertension might occasionally produce headache simulating migraine as an organic symptom during periods of suddenly rising pressure, or, as a relatively insignificant feature, within the syndrome of malignant hypertension. Nevertheless the conclusion appeared clear that the headache which so often accompanies hypertension is usually a product of anxiety deriving solely from the victim's knowledge of his condition. Moreover, it seems almost impossible for a patient who had heard of his "blood pressure" to remain symptom-free. This inquiry was confined to patients afflicted by advanced hypertensive disease. But what of those numerous unfortunates who are so unlucky as to learn of their pressure readings even though the elevation be slight and very possibly transient and insignificant? Need we suppose the mechanism which produces their headaches to be any different?

REFERENCE

[1] Stewart, I. McD. G., *Lancet*, 1953, 1, 1261.

OUR EXPERT replies: I am aware of Dr. Stewart's study and I agree that headache is as unpredictable a development in the hypertensive population as any other complication of hypertension—cardiac, retinal, cerebral, or renal. In a personal series of 89 patients regarded as requiring hypotensive drugs 29 had intensely severe headaches, mostly of the characteristic early morning type, 17 had moderate headaches, and in only 12 were the headaches of the mild "tension-anxiety" type. Severe headaches were notably relieved by effective dosage of hypotensive drugs. Headaches can be quite crippling and were often the presenting symptom before the blood pressure was even measured.

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